Targeted Immune Modulators for Crohn's Disease and Ulcerative Colitis: Update

Systematic Review

February 2020

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Executive Summary

Background

Targeted immune modulators (TIMs) are a category of medications used to treat certain types of immunologic and inflammatory diseases, including Crohn's disease and ulcerative colitis.[1] Although both conditions are classified as inflammatory bowel disease, Crohn's disease is characterized by inflammation involving the full thickness of the bowel wall at any point from mouth to anus, whereas ulcerative colitis is characterized by mucosal ulceration limited to the colon and rectum.[2] Clinical diagnosis of both conditions is most accurately made with colonoscopy.[3]

TIMs work by selectively blocking mechanisms involved in the inflammatory and immune response, although the specific mechanism can vary by TIM agent.[1] There are 4 predominant mechanisms of action in this class of drugs approved or currently being evaluated by the U.S. Food and Drug Administration (FDA) for treatment of Crohn's disease or ulcerative colitis[4,5]:

- Tumor necrosis factor alpha (TNF-α) inhibitors: infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), and golimumab (Simponi)
- Integrin blockers: natalizumab (Tysabri) and vedolizumab (Entyvio)
- Interleukin (IL)-12/23 blockers: ustekinumab (Stelara) and risankizumab (Skyrizi)
- Janus kinase (JAK) inhibitors: upadacitinib (Rinvoq), peficitinib (Smyraf), and tofacitinib (Xeljanz)

Recently, the FDA approved biosimilar agents which are now available for adalimumab (Amjevita, Hyrimoz, and Cyltezo) and infliximab (Renflexis, Inflectra, and Ixifi).

PICOS and Key Questions

This report focuses on adults with Crohn's disease or ulcerative colitis, and identified randomized controlled trials (RCTs) that evaluated the comparative effectiveness and harms of FDA-approved TIM agents and cohort studies that evaluated the comparative harms. Outcomes of interest were measures of clinical improvement and disease remission, quality of life, adverse events (AEs), serious adverse events (SAEs) and other health outcome measures. This report also evaluated the effectiveness and harms (compared to placebo) of selected pipeline TIM agents.

This review addressed 3 key questions:

1. What is the comparative effectiveness of TIMs to treat Crohn's disease and ulcerative colitis?
2. What are the comparative harms of TIMs to treat Crohn's disease and ulcerative colitis?
3. Do the included drugs differ in their effectiveness or harms in the following subgroups: age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or patients with early vs. established disease?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Embase, Cochrane Library, ClinicalTrials.gov, International Standard Randomised Controlled Trials Number (ISRCTN) registry, and several other websites to identify eligible studies from January 1, 2017 through August 20, 2019 with active surveillance of the literature through

December 31, 2019. We rated the methodological quality of eligible studies using standard instruments adapted from national and international quality standards.[6-10] We used OpenEpi (version 3.01) to calculate absolute risk differences (ARD), risk ratios (RR), incident rate ratios (IRR), and associated 95% confidence intervals (CI) based on data provided in the study when these values were not reported by authors. We rated the quality of the body of evidence for each drug comparison and indication (Crohn's disease or ulcerative colitis) for 6 selected outcomes (i.e., quality of life, clinical improvement, overall AEs, withdrawal due to AEs, SAEs, and infections) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[11,12] The previous Drug Effectiveness Review Project (DERP) systematic review on TIMs was segmented into 3 reports; this report is an update only involving medications for indications of Crohn's disease or ulcerative colitis.

Key Findings

We identified 3 new studies[13-15] and carried forward 6 studies[16-21] from the previous report for a total of 9 eligible studies in this update. Four studies evaluated TIM agents exclusively among participants with Crohn's disease;[16,20-22] 2 studies evaluated TIM agents exclusively among participants with ulcerative colitis;[14,17] and 3 studies evaluated TIMs among mixed populations that included participants with Crohn's disease or ulcerative colitis.[13,18,19]

Of the 9 eligible studies, 4 were RCTs[14-16,20] and 5 were cohort studies.[13,17-19,21] Among the 4 RCTs, we rated 1 as poor methodological quality[16] and the rest as fair methodological quality. Among the 5 cohort studies, we rated 1 as poor methodological quality[19] and the rest as fair methodological quality. Outcomes selected for GRADE ratings ranged from very low to moderate quality of evidence with the majority being very low. Generally, outcomes were downgraded for indirectness (i.e., applicability) and very serious imprecision (i.e., wide confidence interval because of small sample size).

Crohn's Disease

- Comparative Effectiveness (Key Question 1) in Crohn's Disease
  - *Adalimumab compared to infliximab (2 RCTs)*—no significant difference in changes in quality of life and clinical improvement; we rated these outcomes as very low quality.

- Comparative Harms (Key Question 2) in Crohn's Disease
  - *Adalimumab compared to infliximab (2 RCTs)*—no significant difference in incidence of AEs; results were too imprecise to draw definitive conclusions about SAEs, withdrawals due to AEs, and infection. We rated these outcomes as very low quality.
  - *Adalimumab compared to certolizumab pegol or infliximab (1 cohort)*—no significant difference in incidence of serious infection. We rated this evidence as very low quality.
  - *Adalimumab vs. infliximab vs. etanercept (2 cohorts)*—significantly higher incidence of tuberculosis with adalimumab (IRRs) 3.5 and 5.6) or infliximab (IRR 4.9 and 6.8) compared to etanercept. No significant differences in harms between adalimumab and infliximab. We rated this evidence as very low quality.

- Effectiveness and Harms of Pipeline Drugs in Crohn's Disease
  - *PF-0236921 compared to placebo (1 RCT)*—significantly higher incidence of clinical improvement and remission at 12 weeks for the 50-mg dosage (47.4% improvement,

27.4% remission), but not for the 10-mg dosage (35.2% improvement, remission not reported) when compared to placebo (28.6% improvement, 10.9% remission). We rated this evidence as moderate and low quality, respectively. No significant differences in improvements in quality of life for 50-mg and 10-mg dosages compared to placebo; we rated this evidence as low quality. No significant difference in incidence of overall AEs; we rated this evidence as moderate quality. No significant difference in SAEs, withdrawals due to AEs, or injection site reactions, but results were too imprecise to draw a definitive conclusion. We rated this evidence as low quality.

- Variation in Effectiveness and Harms by Subgroup (Key Question 3)
  - We did not identify any studies that reported findings by subgroups of interest.

Ulcerative Colitis

- Comparative Effectiveness (Key Question 1) in Ulcerative Colitis
  - *Vedolizumab compared to adalimumab (1 RCT)*—significantly higher incidence of clinical (ARD 8.8%; 95% CI, 2.5% to 15.0%) and endoscopic (ARD 11.9%; 95% CI, 5.3% to 18.5%) remission, and significantly larger improvements in quality of life at 1 year (ARD 9.6%; 95% CI, 2.8% to 16.5%) with vedolizumab (all $P < .05$); we rated this evidence as moderate quality. No significant difference in incidence of corticosteroid-free remission (among those taking steroids at baseline) with vedolizumab; we rated this evidence as low quality.

- Comparative Harms (Key Question 2) in Ulcerative Colitis
  - *Vedolizumab compared to adalimumab (1 RCT)*—marginally significant difference in AEs at 1 year for vedolizumab (RR 0.91; 95% CI, 0.82 to 1.003); we rated this evidence as moderate quality. No significant difference in incidence of SAEs, withdrawals due to AEs, or infections at 1 year for vedolizumab, but results were too imprecise to draw a definitive conclusion; we rated this evidence as low quality.
  - *Infliximab vs. adalimumab (2 cohorts)*—No significant differences in risk of serious infection and overall infections but results were too imprecise to draw a definitive conclusion. We rated this evidence as very low quality.
  - *Adalimumab vs. infliximab vs. etanercept (2 cohorts)*—significantly higher incidence of tuberculosis with adalimumab (IRR 3.5 and 5.6) or infliximab (IRR 4.9 and 6.8) compared to etanercept. No significant difference between adalimumab and infliximab. We rated this evidence as very low quality.

- Variation in Effectiveness and Harms by Subgroup (Key Question 3)
  - We did not identify any studies that reported findings by subgroups of interest.

Ongoing Studies

- We identified 13 ongoing studies (12 RCTs, 1 cohort study). Seven RCTs are in participants with Crohn's disease, 5 RCTs are in participants with ulcerative colitis, and the cohort study is in participants with both conditions. The earliest estimated completion date for any of these studies is March 2021.

Conclusions

The evidence for comparative effectiveness and harms of TIM agents in Crohn's disease is limited to comparisons between adalimumab and certolizumab pegol, etanercept, or infliximab, and we rated nearly all outcomes as low or very low quality of evidence precluding any definitive conclusions. For ulcerative colitis, vedolizumab is more effective compared to adalimumab (moderate quality of evidence) with no difference in AE (moderate to low quality of evidence). Other evidence for comparative harms in ulcerative colitis is limited to comparisons between adalimumab and infliximab or etanercept, and we rated all outcomes as very low quality of evidence precluding any definitive conclusions. We identified 1 pipeline drug (PF-0423691) that is more effective at the 50-mg dosage compared to placebo (moderate quality of evidence for clinical improvement and remission, low quality of evidence for quality of life) and no difference in incidence of AE (low quality of evidence). Thirteen studies of head-to-head comparisons of TIM agents for either Crohn's disease or ulcerative colitis are currently in progress but none will be completed before 2021.

List of Brand Names and Generics

Table 1. Included Drugs and Biosimilars

Generic Name	Trade Name	Mechanism	Route	Approved Population[a]
Adalimumab	Humira	TNF-α Inhibitor	SC	Crohn's disease Ulcerative colitis
Adalimumab-atto	Amjevita	TNF-α Inhibitor	SC	Crohn's disease Ulcerative colitis
Adalimumab-adaz	Hyrimoz	TNF-α Inhibitor	SC	Crohn's disease
Adalimumab-adbm	Cyltezo	TNF-α Inhibitor	SC	Ulcerative colitis
Certolizumab pegol	Cimzia	TNF-α Inhibitor	SC	Crohn's disease
Golimumab	Simponi	TNF-α Inhibitor	SC	Ulcerative colitis
Infliximab	Remicade	TNF-α Inhibitor	IV	Crohn's disease Ulcerative colitis
Infliximab-abda	Renflexis	TNF-α Inhibitor	IV	Crohn's disease Ulcerative colitis
Infliximab-dyyb	Inflectra	TNF-α Inhibitor	IV	Crohn's disease Ulcerative colitis
Infliximab-qbtx	Ixifi	TNF-α Inhibitor	IV	Crohn's disease Ulcerative colitis
Natalizumab	Tysabri	α4 integrin inhibitor	IV	Crohn's disease
Risankizumab	Skyrizi	IL-23 Inhibitor	SC	Plaque psoriasis[b]
Tofacitinib	Xeljanz	JAK inhibitor	PO	Ulcerative colitis
Upadacitinib	Rinvoq	JAK Inhibitor	PO	Rheumatoid arthritis[c]
Ustekinumab	Stelara	IL-12/23 p40 Inhibitor	Initial dose IV then SC	Crohn's disease Ulcerative colitis
Vedolizumab	Entyvio	α4β7 integrin Inhibitor	IV	Crohn's disease Ulcerative colitis
Pipeline Drugs				
Peficitinib	Smyraf	JAK Inhibitor	PO	Under investigation
PF-04236921	NA	IL-6 Inhibitor	SC	Under investigation

Notes. [a] Details of approved indications for each drug can be found in the full prescribing information. Some agents are approved for indications other than inflammatory bowel disease; [b] Risankizumab is approved for moderate-to-severe plaque psoriasis and is currently being evaluated for use in Crohn's disease and ulcerative colitis; [c] Upadacitinib is approved for moderate-to-severe rheumatoid arthritis and is currently being evaluated for use in Crohn's disease and ulcerative colitis. Abbreviations. IL: interleukin; IV: intravenous; JAK: Janus kinase; NA: not applicable; PO: per os (orally); SC: subcutaneous; TNF-α: tumor necrosis factor alpha.

Background

Targeted immune modulators (TIMs) are a category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis. The U.S. Food and Drug Administration (FDA) approved the first TIM, infliximab, for Crohn's disease in 1998,[23] and since then have approved numerous additional agents, including recently approved biosimilar TIM agents. Table 1 summarizes TIMs currently available in the U.S. for treatment of Crohn's disease and ulcerative colitis.

TIMs work by selectively blocking mechanisms involved in the inflammatory and immune response.[1] Tumor necrosis factor alpha (TNF-α) inhibitors block specific proinflammatory mediators known as cytokines. Of the TIMs evaluated for use in Crohn's disease and ulcerative colitis, adalimumab, certolizumab pegol, golimumab, and infliximab all bind to both the circulating and transmembrane forms of TNF-α, inhibiting its biological activity.[1] Biosimilars are available for both adalimumab (Amjevita, Hyrimoz, Cyltezo) and infliximab (Renflexis, Inflectra, Ixifi). Vedolizumab and natalizumab are humanized monoclonal antibodies that target the α-4 integrin chain.[4] Ustekinumab is a human monoclonal antibody that binds to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines.[4] Tofacitinib is a novel orally-administered small molecule directed against the Janus kinase/signal transducer and activator of transcription (JAK/STAT) proteins pathway.[5]

In addition to the FDA-approved TIMs with an indication for Crohn's disease, ulcerative colitis, or both, we considered 4 additional drugs in this update that are currently being evaluated and have the potential for approval for the treatment of Crohn, ulcerative colitis, or both. Risankizumab is a humanized monoclonal antibody that selectively binds to the p19 submit of IL-23 and is currently FDA-approved for the treatment of moderate-to-severe plaque psoriasis.[4] Upadacitinib is an oral JAK inhibitor and is currently FDA-approved for the treatment of moderate-to-severe rheumatoid arthritis in patients with an inadequate response or intolerance to methotrexate.[5] Peficitinib is also an oral JAK inhibitor; it is approved for the treatment of rheumatoid arthritis in Japan but not yet FDA-approved for use in the United States.[24] Lastly, we identified PF-04236921, an IL-6 inhibitor currently under investigation.

Crohn's Disease

Crohn's disease is a condition of the bowel causing inflammation involving the full thickness of the bowel wall.[2] This may occur at any point from the mouth to the anus. This chronic inflammation leads to fibrosis and obstructive symptoms with sinus tracts and fistulae. Abdominal pain and diarrhea, with or without bleeding, are characteristic of the disease. Constitutional symptoms are very common, predominantly fatigue and weight loss. Extraintestinal symptoms may occur and include inflammatory eye disease, arthritis, and sclerosing cholangitis. Clinicians diagnose the condition based on history and physical examination. They use endoscopy and biopsy of the involved segment of the gastrointestinal tract to confirm the diagnosis.[3]

The treatment goals for Crohn's disease are to control the inflammation, maintain remission, and prevent complications.[25,26] Newer goal therapy involves the induction and maintenance of mucosal (and histologic) healing.[27] Five-aminosalicylate drugs or antibiotics may control mild

disease, but if the disease is resistant to these interventions or is more severe, physicians frequently prescribe corticosteroids such as prednisone and budesonide.[25] If symptoms persist despite steroids, or if the disease flares upon tapering the steroids, clinicians often institute immunomodulatory agents (azathioprine, 6-mercaptopurine, and methotrexate).[26] TIMs may be warranted in patients with moderate-to-severe active Crohn's disease who have had inadequate response to conventional therapy; TIMs are also sometimes used before other therapies.[26 27]

Ulcerative Colitis

Ulcerative colitis is a chronic inflammatory bowel disease characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain, and is limited to the colon and rectal areas.[2] The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Clinical diagnosis is most accurately made with colonoscopy or sigmoidoscopy.[3]

Treatment aims to reduce and maintain remission of symptoms and inflammation and prevent complications.[23] Topically-applied rectal treatments may reach distal disease, which is limited to the region below the descending colon.[28] Oral and/or topical 5-aminosalicylate drugs may control mild disease.[28] If the disease is resistant to these interventions or is more severe, corticosteroids are frequently used.[29] In addition, the FDA has approved some TIMs for treatment of moderate-to-severe active ulcerative colitis after the failure of conventional therapy.[29]

PICOS

Population

- Adults with Crohn's disease
- Adults with ulcerative colitis

Interventions

- TIMs and respective biosimilars that have FDA approval for the treatment of Crohn's disease or ulcerative colitis and select pipeline drugs likely to be approved soon (Table 1)

Comparators

- For FDA-approved drugs: another listed TIM intervention (head-to-head comparison)
- For pipeline drugs: any listed TIM, standard of care, placebo

Outcomes

- Health outcomes
  - Quality of life
  - Functional capacity
  - Productivity, ability to sustain employment
  - Clinical improvement
  - Disease remission
  - Pain
  - Reduction in disease-related hospitalizations
  - Reduction in disease-specific mortality
  - Rebound/flare
  - Steroid withdrawal

- Harms
  - Overall adverse events (AEs)
  - Withdrawals due to AE
  - Serious adverse events (SAEs)
  - Specific AE (e.g., lymphoma, all malignancies, serious infectious diseases, herpes zoster, opportunistic infections, congestive heart failure)
  - Mortality

Study Designs

- RCTs with ≥ 12-week study duration
- Retrospective and prospective cohort studies comparing an intervention type to another for outcomes on harms
  - > 12-week study duration
  - Minimum total sample size of 1,000

Key Questions

1. What is the comparative effectiveness of TIMs to treat Crohn's disease and ulcerative colitis?
2. What are the comparative harms of TIMs to treat Crohn's disease and ulcerative colitis?
3. Do the included drugs differ in their effectiveness or harms in the following subgroups: age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early vs. established disease?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Embase, Cochrane Library, ClinicalTrials.gov, the International Standard Randomised Controlled Trials Number (ISRCTN) registry, and several other websites to identify eligible studies from January 1, 2017 through August 20, 2019, with active surveillance of the literature through December 31, 2019. We rated the methodological quality of eligible studies using standard instruments adapted from national and international quality standards.[6-10] We used OpenEpi (version 3.01) to calculate absolute risk differences (ARD), risk ratios (RR), incident rate ratios (IRR) and associated 95% confidence intervals (CI) based on data provided in the study when these values were not reported by authors. We rated the quality of the body of evidence for each drug comparison and indication (Crohn's disease or ulcerative colitis) for 6 selected outcomes (i.e., quality of life, clinical improvement, overall AEs, withdrawal due to AEs, SAEs, and infections) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[11,12] The previous Drug Effectiveness Review Project (DERP) systematic review on TIMs was segmented into 3 reports; this report is an update and only involves medications for indications of Crohn's disease or ulcerative colitis.

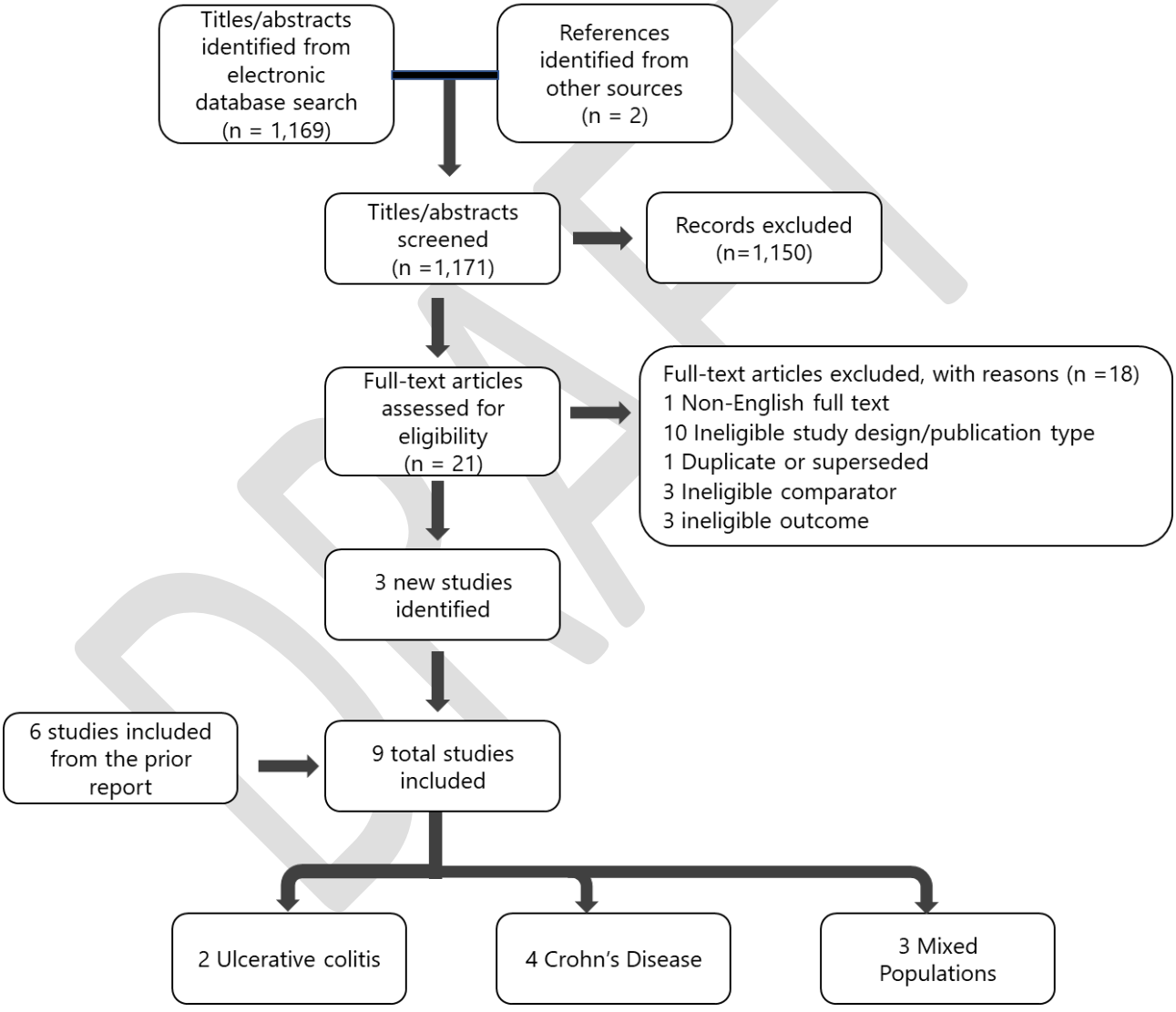
Findings

We identified 3 new studies[13-15] and carried forward 6 studies from the prior review[16-21] for a total of 9 eligible studies in this update (Figure 1 and Appendix F) that report on comparative effectiveness (Key Question 1) or comparative harms (Key Question 2). We excluded 1 study that was included in the prior report because it did not meet inclusion criteria for this update: the sample size of this cohort study was only 275 participants.[30] Appendix G provides the

bibliography of studies identified in the updated search but that were excluded during our full-text review.

Four studies evaluated TIM agents exclusively among participants with Crohn's disease;[16,20-22] 2 studies evaluated TIM agents exclusively among participants with ulcerative colitis;[14,17] and 3 studies evaluated TIMs among mixed populations that included participants with Crohn's disease, ulcerative colitis, or other autoimmune disorders.[13,18,19] We did not identify any studies that addressed differences in effectiveness or harms by subgroup (Key Question 3).

Figure 1. Literature Flow Diagram



Crohn's Disease

We identified 2 RCTs evaluating the comparative effectiveness and harms of TIMs,[16,20] 1 RCT evaluating the effectiveness and harms of a pipeline TIM,[15] and 4 cohort studies evaluating the

comparative harms of TIMs.[13,18,19,21] Table 2 shows the Summary of Findings (GRADE) for these comparisons. Appendix B, Tables B1-B3, provide detailed study characteristics and findings, and Appendix C, Table C1 provides detailed evidence profiles. Appendix D describes outcome measures used in the included RCTs.

Table 2. Summary of Findings (GRADE) of Targeted Immune Modulators for Crohn's Disease

Outcome	Quality of Evidence	Relationship	Rationale
Adalimumab vs. Infliximab			
Quality of life (1 RCT[20])	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 2 levels for very serious imprecision
Clinical improvement (1 RCT[16])	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Overall AEs (1 RCT[20])	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 2 levels for very serious imprecision
Withdrawal due to AEs (1 RCT[20])	Very low ●○○○	Relationship cannot be determined	
SAEs (1 RCT[20])	Very low ●○○○	Relationship cannot be determined	
Infections (1 cohort study[13])	Very low ●○○○	Relationship cannot be determined	Downgraded for indirectness and imprecision
PF-04236921 vs. Placebo			
Clinical improvement at 12 weeks (CDAI-70) (1 RCT[15])	Moderate ●●●○	Greater improvement with 50 mg (vs. placebo); no difference for 10 mg (vs. placebo)	Downgraded 1 level for imprecision
Clinical remission at 12 weeks (CDAI < 150) (1 RCT[15])	Low ●●○○	Higher incidence with 50 mg (vs. placebo); no difference for 10 mg (vs. placebo)	Downgraded 2 levels for very serious imprecision
Quality of life (IBDQ) at 12 weeks (1 RCT[15])	Low ●●○○	No difference between 50 or 10 mg (vs. placebo)	Downgraded 2 levels for very serious imprecision
Overall AEs at 12 weeks (1 RCT[15])	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs, withdrawals due to AE, injection site reactions at 12 weeks (1 RCT[15])	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Adalimumab vs. Certolizumab vs. Infliximab			
Serious infection (1 cohort study[21])	Very low ●○○○	No difference among groups	Downgraded for indirectness and imprecision

Outcome	Quality of Evidence	Relationship	Rationale
Adalimumab vs. Infliximab vs. Etanercept			
Incidence of tuberculosis (2 cohort studies[18,19])	Very low ●○○○	Higher incidence with adalimumab and infliximab compared to etanercept	Downgraded for indirectness, study limitations, and imprecision

Note. For methods and interpretation of GRADE ratings, see Appendix A. Abbreviations. AE: adverse events; CDAI: Crohn's Disease Activity Index; CDAI-70: proportion of patients achieving ≥ 70-point reduction in CDAI score; IBDQ: Inflammatory Bowel Disease Questionnaire; RCT: randomized controlled trial; SAE: serious adverse events.

Effectiveness (Key Question 1)

We included 3 RCTs;[15,16,20] 1 of these studies was new to this update.[15] We rated 2 RCTs as fair methodological quality[15,20] and 1 RCT as poor methodological quality.[16]

Adalimumab Compared to Infliximab

We included 2 open-label, randomized, head-to-head trials[16,20] comparing subcutaneous adalimumab with intravenous infliximab for the treatment of Crohn's disease. Table 3 summarizes these trials. Van Assche et al.[20] reported that the authors worked independently on the study; nevertheless, most authors declared competing interests due to financial grants from the pharmaceutical industry, including both companies producing the investigated drugs. Tursi et al. did not report sponsorship information.[16]

Van Assche et al. was a fair-methodological-quality, open-label switch trial that randomized 73 patients with ongoing infliximab maintenance therapy to continue their current infliximab regimen (5 mg/kg intravenously every 6 to 8 weeks) for 56 weeks or to switch to adalimumab (80 mg subcutaneously at inclusion and 40 mg subcutaneously every other week for 54 weeks).[20] The median Inflammatory Bowel Disease Questionnaire (IBDQ) scores were not different between groups throughout the study.[20]

The poor-methodological-quality RCT reported by Tursi et al. was conducted among adults with Crohn's disease who were treated for 12 months after ileocolonic resection; these patients were at high risk for postoperative recurrence.[16] This study reported no statistically significant differences between adalimumab- and infliximab-treated patients regarding clinical (10% vs. 10%), endoscopic (10% vs. 20%), and histological (20% vs. 30%) recurrence after 12 months.[16]

PF-04236921 Compared to Placebo

We identified 1 fair-methodological-quality RCT comparing a pipeline drug (PF-04236921) with placebo.[15] Table 3 summarizes this study. Pfizer funded this study, and 5 authors were Pfizer employees who were involved in study design as well as data collection, analysis, and interpretation. The study enrolled adults with moderate-to-severe Crohn's disease who had failed or were intolerant to 1 or more anti-TNF-α agents, and compared 3 doses (10 mg, 50 mg and 200 mg administered subcutaneously on days 1 and 28) of PF-04236921 with placebo.[15] The 200-mg dosage was not included in analysis because this study arm was stopped early due to fatalities in patients with lupus who were treated with this dosage in a separate trial.

The primary outcome was the proportion of patients achieving ≥ 70-point reduction in their Crohn's Disease Activity Index score (CDAI-70). Compared to placebo, the 50-mg dosage produced a significantly greater CDAI-70 response at both 8 weeks (49% vs. 31%; *P* < .05) and at 12 weeks (47% vs. 29%; *P* < .05).[15] In contrast, the 10-mg dosage showed no significant difference at either 8 weeks (35% vs. 31%; *P* > .05) or 12 weeks (35% vs. 29%; *P* > .05).[15]

Secondary outcomes included CDAI-100 response, CDAI remission (CDAI score < 150), mean change in CDAI scores, IBDQ, and EuroQol 5-dimension assessment instrument (EQ-5D). Significant differences were reported for CDAI-100 response and CDAI remission between the 50-mg group and placebo (response rates depicted on a figure only, P < .05). No statistically significant effect in this outcome was reported for the 10-mg group compared to placebo at any time point. At 12 weeks, a significantly greater percentage of participants in the 50-mg dosage active treatment group achieved remission as defined by CDAI score < 150 (27 % vs. 11%; *P* < .05) compared to placebo.[15] No significant differences were observed for either dosages compared to placebo on the IBDQ or the EQ-5D (1-sided P > .05).

Table 3. Evidence Table for Efficacy Outcomes in Adults for Targeted Immune Modulators for Crohn's Disease (Brief Version)

Authors, Year	Study Design Study Quality	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results
Adalimumab vs. Infliximab								
Van Assche et al.,[20] 2012	RCT (switch study) Fair	73	12 months	Adalimumab vs. infliximab	Patient preference; need of rescue therapy or treatment termination	CDAI > 100 above baseline; IBDQ	Adults with luminal CD (CDAI < 200) treated with infliximab for at least 6 weeks of the last 6 months with complete response	No statistically significant difference in IBDQ scores
Tursi et al.,[16] 2014	RCT Poor	20	12 months	Adalimumab vs. infliximab	Endoscopic, histological, and clinical recurrence after therapy	NR	Adults with CD treated with adalimumab or infliximab after ileocolonic resection for 12 months; CD patients with high risk for postoperative recurrence	No statistically significant differences between adalimumab-and infliximab-treated groups regarding endoscopic recurrence, histological disease activity, and clinical recurrence rates
PF-04236921 vs. Placebo								
Danese et al.,[15] 2017	RCT Fair	249	3 months	Placebo vs. PF-04236921 (10 mg, 50 mg, 200 mg)	CDAI-70 response at weeks 8 or 12	CDAI-100 response, CDAI remission (score < 150), mean changes from baseline in CDAI scores, IBDQ, EQ-5D	Adults with moderate-to-severe CD who failed at least 1 anti-TNF-α therapy	50-mg dosage had statistically significantly greater CDAI-70 response compared to placebo at weeks 8 and 12, no statistically significant difference for 10-mg dosage. The 200-mg dosage was not included in analyses[a]

Note. [a]*The 200-mg dosage group was stopped early due to fatalities in participants with lupus at this dosage in a separate trial. Abbreviations. CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CDAI-70: proportion of patients achieving ≥ 70-point reduction in CDAI score; CDAI-100: proportion of patients achieving ≥ 100-point reduction in CDAI score; EQ-5D: EuroQol 5-dimension assessment instrument; IBDQ: Inflammatory Bowel Disease Questionnaire; NR: not reported; RCT: randomized controlled trial; TNF-α: tumor necrosis factor alpha.*

Harms (Key Question 2)

We included 2 RCTs, both of fair methodological quality[15,20] and 4 cohort studies.[13,18,19,21] We rated all but 1 cohort study as fair methodological quality.[19] One RCT[15] and 1 cohort study[13] were new to this update.

Findings from RCTs

Table 4 and Table 5 summarize the harm findings from RCTs. Van Assche et al. (fair-quality RCT) reported no significant differences in harms other than a possible increase in injection site/infusion reactions with adalimumab compared to infliximab, though results were very imprecise (RR, 8.22; 95% CI, 1.08 to 62.46).[20]

When comparing PF-04236921 with placebo, Danese et al. reported no statistically significant differences for AEs, SAEs, withdrawals due to AE, or injection site reactions.[15] Common AEs included worsening of Crohn's disease, abdominal pain, headache, and nasopharyngitis. One death occurred in the 50-mg dosage group.[15]

Findings from Observational Studies

Table 6 summarizes the harm findings from cohort studies.

Di Domenicantonio et al. was a fair-methodological-quality study using administrative and registry data among 1,400 patients in Italy that compared infliximab with adalimumab among a population with either Crohn's disease or ulcerative colitis. Among the population with Crohn's disease (N = 872), the authors reported no difference in incidence of infusion reactions (0.8%) and a numerically higher incidence of infections with infliximab compared to adalimumab (adjusted hazard ratio [aHR], 1.63; 95% CI, 0.61 to 4.34), but this result was not statistically significant and the estimate was very imprecise.[13]

In two cohort studies, Winthrop et al.[19] and Jung et al.,[18] compared adalimumab with etanercept and infliximab. Both studies were conducted among mixed populations that included participants with Crohn's disease, but also enrolled participants with other autoimmune diseases for which TIMs are indicated. We rated 1 study as fair methodological quality[18] and 1 study as poor methodological quality.[19] Winthrop et al. conducted a study in over 8,000 Kaiser Permanente beneficiaries and found a significantly higher incidence rate tuberculosis for adalimumab (incident rate ratio [IRR], 5.6) and infliximab (IRR, 4.9) compared to etanercept.[19] Jung et al. used data from the Health Insurance Review and Assessment Service in South Korea; this study also reported a statistically significant higher risk of tuberculosis for adalimumab and infliximab compared to etanercept.[18]

Singh et al. reported a cohort study comparing adalimumab with certolizumab pegol and infliximab using administrative and claims data.[21] We rated this study as fair methodological quality. The American College of Gastroenterology sponsored this study, with additional investigator support from the National Institutes of Health. This study was conducted among over 3,000 persons using data from OptumLabs, which includes privately insured and Medicare beneficiaries in the United States.[21] The risk of serious infection was not statistically significantly different among the 3 TIM agents; however, results were imprecise.

Table 4. Summary of Adverse Events from RCTs in Adults Receiving TIMs for Crohn's Disease

Authors, Year, Trial Name	Study Design Study Quality	N	Duration	Comparison	Population	Results
Van Assche, et al.,[20] 2012 None	RCT Fair	73	12 months	Adalimumab vs. infliximab	Crohn's disease	No statistically significant differences in harms
Danese et al.,[15] 2017 ANDANTE I and II	RCT Fair	249	3 months	Placebo vs. PF-04236921 10 mg, PF-04236921 50 mg, PF-04236921 200 mg	Moderate-to-severe Crohn's disease who failed at least 1 anti-TNF-α therapy.	50-mg and 10-mg dosage groups had no statistically significant difference in incidence of any AE or SAEs compared to placebo, but numerically higher (but statistically not different) incidence of severe AE; 1 death occurred in the 50-mg dosage group. The 200-mg dosage was not included in the analysis[a]

Note. [a] *The 200-mg dosage group was stopped early due to fatalities in participants with lupus at this dosage in a separate trial. Abbreviations: AE: adverse event; RCT: randomized controlled trial; TNF-α: tumor necrosis factor alpha; SAE: serious adverse event.*

Table 5. Head-to-Head Comparisons of TIMs in RCTs for General Tolerability in Crohn's Disease

Authors, Year Trial Name	Overall AEs RR (95% CI)	Withdrawal Due to AEs RR (95% CI)	SAEs RR (95% CI)	Injection Site Reactions/ Infusion Reactions RR (95% CI)	Study Quality
Adalimumab vs. Infliximab					
Van Assche et al.,[20] 2012 None	1.14 (0.89 to 1.46)[a,b]	6.17 (0.78 to 48.71)[a, b]	9.95 (0.57 to 174.1)[a,b]	8.22 (1.08 to 62.46)[a,b]	Fair
PF-04236921 vs. Placebo					
Danese et al.,[15] 2017 ANDANTE I and II	10 mg: 0.98 (0.88 to 1.10)[b] 50 mg: 0.89 (0.78 to 1.02)[b]	10 mg: 0.88 (0.31 to 2.5)[b] 50 mg: 0.83 (0.30 to 2.4)[b]	Severe AEs[c] 10 mg: 2.5 (0.92 to 6.6)[b] 50 mg: 2.3 (0.87 to 6.3)[b] SAEs[c] 10 mg: 0.80 (0.32 to 2.0)[b] 50 mg: 0.97 (0.41 to 2.3)[b]	10 mg: 0.51 (0.10 to 2.7)[b] 50 mg: 1.70 (0.52 to 5.6)[b]	Fair

Notes. [a] This trial recruited patients with a response to infliximab and then randomized them to continue infliximab or switch to adalimumab and therefore is a selected population of patients who have tolerated infliximab therapy for at least 6 months. [b] Indicates a calculated value. [c] Study did not describe difference between what they considered severe AE vs. SAE. Abbreviations. AE: adverse event; CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; TIM: targeted immune modulator.

Table 6. Summary of Observational Studies of AEs in Adults Receiving TIMs for Crohn's Disease

Authors, Year	Number of Patients	Follow-up	Comparison	Population	Results	Study Quality
OptumLabs Data Warehouse (Privately Insured and Medicare); United States						
Singh et al.,[21] 2016	3,205	19 months median	Adalimumab vs. certolizumab pegol vs. infliximab	CD	Risk of serious infection • Infliximab vs. adalimumab: aHR 0.88; 95% CI, 0.48 to 1.64 • Infliximab vs. certolizumab pegol: aHR 0.47; 95% CI, 0.08 to 2.75 • Certolizumab vs. adalimumab: aHR 2.06; 95% CI, 0.98 to 4.35	Fair
Hospital Information System, Payment Exemptions Register, Regional Drug Claims Register, and the Population Registry; Italy						
Di Domenicantonio et al.,[13] 2018	872 with CD	2 years	Adalimumab vs. infliximab	CD subgroup	No difference incidence of infusion reaction (0.8%); higher risk of infection with infliximab (aHR 1.63; 95% CI, 0.61 to 4.34) compared to adalimumab but results imprecise	Fair
HIRA (Health Insurance Review and Assessment Service); South Korea						
Jung et al., 2015[18]	8,421	10,021 person-years	Adalimumab vs. etanercept vs. iInfliximab	Mixed	Higher risk for tuberculosis with adalimumab (IRR 3.45; 95% CI, 1.82 to 6.55) and infliximab (IRR 6.80; 95% CI, 3.74 to 12.37) compared to etanercept	Fair
Kaiser (Kaiser Permanente Northern California); United States						
Winthrop et al., 2013[19]	8,418	20,330 person-years	Adalimumab vs. etanercept vs. infliximab	Mixed	Higher incidence of tuberculosis for adalimumab (IRR 5.6; 95% CI, 3.3 to 9.2) and infliximab (IRR 4.9; 95% CI, 3.0 to 8.5) compared to etanercept. No difference in incidence between adalimumab and infliximab (IRR 1.1; 95% CI, 0.81 to 1.5)	Poor

Abbreviations. AE: adverse event; aHR: adjusted hazard ratio; CD: Crohn's disease; CI: confidence interval; IRR: incident rate ratio; TIM: targeted immune modulator.

Ulcerative Colitis

We identified 1 RCT evaluating the comparative effectiveness and harms of TIMs[14] and 4 cohort studies evaluating the comparative harms of TIMs.[13,17-19] Table 7 includes the Summary of Findings (GRADE) for these comparisons. Appendix B, Tables B1-B3, provide detailed study characteristics and findings. Appendix C, Table C2, provides detailed evidence profiles. Appendix D describes outcome measures used in included RCTs.

Table 7. Summary of Findings (GRADE) of Targeted Immune Modulators for Ulcerative Colitis

Outcome	Quality of Evidence	Relationship	Rationale
Vedolizumab vs. Adalimumab			
Clinical and endoscopic remission at 1 year (1 RCT[14])	Moderate ●●●○	Higher incidence with vedolizumab	Downgraded 1 level for imprecision
Corticosteroid-free remission[a] at 1 year (1 RCT[14])	Low ●●○○	No difference	Downgraded 2 levels for very serious imprecision
Quality of life at 1 year (1 RCT[14])	Moderate ●●●○	Larger improvements with vedolizumab	Downgraded 1 level for imprecision
Overall AE at 1 year (1 RCT[14])	Moderate ●●●○	Marginally lower incidence with vedolizumab	Downgraded 1 level for imprecision
SAE, withdrawals due to AE at 1 year (1 RCT[14])	Low ●●○○	No difference	Downgraded 2 levels for very serious imprecision
Infections at 1 year (1 RCT[14])	Low ●●○○	No difference	Downgraded 2 levels for very serious imprecision
Infliximab vs. Adalimumab			
Serious infection (1 cohort study[17])	Very low ●○○○	May be lower incidence, but results too imprecise for definitive conclusion	Downgraded for indirectness and for imprecision
Infections (1 cohort study[13])	Very low ●○○○	May be lower incidence, but results too imprecise for definitive conclusion	Downgraded for indirectness and imprecision
Adalimumab vs. Infliximab vs. Etanercept			
Incidence of tuberculosis (2 cohort studies[18,19])	Very low ●○○○	Higher incidence with adalimumab and infliximab compared to etanercept	Downgraded for study limitations, indirectness, and imprecision

Note. For methods and interpretation of GRADE ratings, see Appendix A. [a]Among those on steroids at baseline. Abbreviations. AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event.

Effectiveness (Key Question 1)

We included 1 fair-methodological-quality RCT, which was new to this update.[14]

Vedolizumab Compared to Adalimumab

One RCT[14] (VARSITY) compared vedolizumab to adalimumab among participants with moderate-to-severe ulcerative colitis and followed participants for 1 year. Table 8 summarizes this study,

which was sponsored by the manufacturer. We rated this study as fair quality primarily because of extensive manufacturer involvement in study design and execution.

At 1 year, participants randomized to vedolizumab had a higher incidence of achieving a clinical remission (31% vs. 23%; ARD, 9%; 95% CI, 3% to 15%) and endoscopic remission (40% vs. 28%; ARD, 12%; 95% CI, 5% to 19%) compared to adalimumab.[14] However, fewer participants in the vedolizumab group had a corticosteroid-free clinical remission, though this result was not statistically significant (13% vs. 22%; ARD, -9%; 95% CI, -19% to 0.4%).[14] Participants who were randomized to vedolizumab had statistically significantly larger improvements in quality of life compared to those allocated to adalimumab (Appendix B, Table B2).[14]

Harms (Key Question 2)

We included 1-fair methodological-quality RCT[14] and 4 cohort studies.[13,17-19] One cohort study was of poor methodological quality;[19] the rest were fair methodological quality. The RCT[14] and 1 of the cohort studies[13] was new to this update.

Findings from RCTs

Table 9 and Table 10 summarize the harm outcomes from the VARSITY RCT.[14] The incidence of AEs, SAEs, and withdrawals due to AEs was numerically lower for vedolizumab compared to adalimumab, but these findings were not statistically significant. One death occurred in the vedolizumab group but was not considered to be related to the study drug. The incidence of infections was not statistically different between groups (34.6 per 100 person-years vs. 23.4 per 100 person-years; calculated IRR, 1.5; 95% CI, 0.89 to 2.5; *P* = .12)

Findings from Observational Studies

Table 11 summarizes the harm findings from cohort studies.

Two cohort studies compared adalimumab with infliximab.[13,17] We assessed both studies as fair methodological quality. Both studies (1 conduced in the U.S. and 1 conducted in Italy) were based on administrative and claims data.[13,17] The American College of Gastroenterology funded the study by Singh et al.[17] and the National Institutes for Health provided additional investigator support. This study was conducted among 1,400 privately insured and Medicare beneficiaries using OptumLabs data.[30] This study reported that the risk of serious infections was lower for infliximab compared to adalimumab, but results were not precise (aHR, 0.62; 95% CI, 0.29 to 1.34). The study reported by Di Domenicantonio et al.[13] used administrative and registry data from 1,432 patients in Italy; the funding source for this study was not reported. This study reported a lower incidence of infections with infliximab compared to adalimumab, but results were imprecise (aHR, 0.68; 95% CI, 0.19 to 2.44).[13] This study reported a similar incidence of infusion reactions for both agents (1.9% vs. 0%).

We identified 2 cohort studies comparing adalimumab with infliximab and etanercept.[18,19] Both studies were conducted among mixed populations that included participants with ulcerative colitis, but also enrolled participants with other autoimmune diseases for which TIMs are indicated. We rated 1 study as fair methodological quality[18] and 1 study as poor methodological quality.[19] Winthrop et al.[19] conducted a study in over 8,000 Kaiser Permanente beneficiaries and found a significantly higher incidence rate of tuberculosis for adalimumab (IRR, 5.6) and

infliximab (IRR, 4.9) compared to etanercept. Jung et al.[18] used data from the Health Insurance Review and Assessment Service in South Korea; this study also found a higher risk of tuberculosis for adalimumab and infliximab compared to etanercept.

Table 8. Evidence Table for Efficacy Outcomes in Adults from TIMs for Ulcerative Colitis (Brief Version)

Authors, Year Trial Name	Study Design Study Quality	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results
Vedolizumab vs. Adalimumab								
Sands et al.,[14] 2019 VARSITY	RCT Fair	769	52 weeks	Vedolizumab 300 mg IV at periodic intervals[a]; adalimumab 40 mg SC every 2 weeks[b]	Clinical remission (Mayo score)	Endoscopic improvement, corticosteroid-free remission	Adults ages 18 to 85 with moderate-to-severe ulcerative colitis who had not previously used a TNF-α inhibitor and did not respond to conventional treatments	Vedolizumab superior to adalimumab for clinical remission and endoscopic improvement; corticosteroid-free remission was numerically but not statistically higher for adalimumab compared to vedolizumab

Notes. [a]Day 1, weeks 2, 6, 14, 22, 30, 38, 46; [b]After initial 160-mg dose in week 1 and 80-mg dose in week 2. Abbreviations. IV: intravenous; RCT: randomized controlled trial; SC: subcutaneous; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha.

Table 9. Summary of AEs from RCTs in Adults Receiving TIMs for Ulcerative Colitis

Authors, Year Trial Name	Study Design Study Quality	N	Duration	Comparison	Population	Results
Vedolizumab vs. Adalimumab						
Sands et al.,[14] 2019 VARSITY	RCT Fair	769	52 weeks	Vedolizumab 300 mg IV at periodic intervals[a]; adalimumab 40 mg SC every 2 weeks[b]	Adults ages 18 to 85 with moderate-to-severe ulcerative colitis who had not previously used a TNF-α inhibitor and did not respond to conventional treatments	No statistically significant differences between groups in overall AE, SAE, or withdrawals due to AE.

Notes. [a]Day 1, weeks 2, 6, 14, 22, 30, 38, 46; [b]After initial 160-mg dose in week 1 and 80-mg dose in week 2. Abbreviations. AE: adverse event; IV: intravenous; RCT: randomized controlled trial; SAE: serious adverse event; SC: subcutaneous; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha.

Table 10. Head-to-Head Comparisons of TIMs in RCTs for General Tolerability in Adults with Ulcerative Colitis

Authors, Year Trial Name	Overall Adverse Events RR (95% CI)	Withdrawal Due to Adverse Events RR (95% CI)	Serious Adverse Events RR (95% CI)	Injection Site Reactions/Infusion Reactions RR (95% CI)	Study Quality
Vedolizumab vs. adalimumab					
Sands et al.,[14] 2019 VARSITY	0.91 (0.82 to 1.00)	0.69 (0.38 to 1.25)	0.80 (0.55 to 1.17)	NR	Fair

Abbreviations. CI: confidence interval; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; TIM: targeted immune modulator.

Table 11. Summary of Observational Studies of Adverse Events in Adults Receiving TIMs for Ulcerative Colitis

Authors, Year	Number of Patients	Follow-up	Comparison	Population	Results	Study Quality
OptumLabs Data Warehouse (Privately Insured and Medicare); United States						
Singh et al.,[17] 2016	1,400	19 months median	Infliximab vs. adalimumab	Ulcerative colitis	Lower risk of serious infections (aHR, 0.62; 95% CI, 0.29 to 1.34), but results imprecise	Fair
Hospital Information System, Payment Exemptions Register, Regional Drug Claims Register, and the Population Registry; Italy						
Di Domenicantonio et al.,[13] 2018	560 with ulcerative colitis	2 years	Infliximab vs. adalimumab	Ulcerative colitis subgroup	Similar incidence of infusion/injection reaction (1.9% vs. 0%); lower risk of infection (aHR, 0.68; 95% CI, 0.19 to 2.44), but results imprecise	Fair
HIRA (Health Insurance Review and Assessment Service); South Korea						
Jung et al.,[18] 2015	8,421	10,021 person-years	Adalimumab vs. etanercept vs. infliximab	Mixed[a]	Higher risk for tuberculosis with adalimumab (IRR, 3.45; 95% CI, 1.82 to 6.55) and infliximab (IRR, 6.80; 95% CI, 3.74 to 12.37) compared to etanercept	Fair
Kaiser Permanente Northern California; United States						
Winthrop et al.,[19] 2013	8,418	20,330 person-years	Adalimumab vs. etanercept vs. infliximab	Mixed[b]	Higher crude incidence of tuberculosis for adalimumab and infliximab compared to etanercept, but results very imprecise	Poor

Notes. [a] Includes participants prescribed a TNF-α inhibitor, the specific indications were not reported. [b] Includes participants prescribed a TNF-α inhibitor for rheumatoid arthritis, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, or ankylosing spondylitis. Abbreviations. aHR: adjusted hazard ratio; CI: confidence interval; IRR: incidence rate ratio; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha.

Ongoing Studies

We identified 13 ongoing studies evaluating the comparative effectiveness or harms of TIM agents (Table 12). Twelve of these studies are RCTs while 1 is a cohort study. Seven RCTs include participants with Crohn's disease, 5 RCTs include participants with ulcerative colitis, and the cohort study includes participants with both Crohn's disease and ulcerative colitis. Industry organizations are sponsoring all but 1 study. The earliest estimated completion date for any of these studies is March 2021.

Table 12. Ongoing Studies of Comparative Effectiveness and Harms of TIM Agents in Crohn's Disease or Ulcerative Colitis

Registration Number Trial Name Phase	Treatment Groups Blinded vs. Open	N Enrolled Treatment Duration	Study Completion Date	Primary Outcome(s)
Adalimumab vs. Ustekinumab (Crohn's Disease)				
NCT03464136 Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year (SEAVUE) Phase 3b	Adalimumab 40 mg; ustekinumab 6 mg/kg loading dose then 90 mg Blinded	N = 350 (estimated) 52 weeks	June 2021 (estimated)	Percent of participants with clinical remission at week 52
Vedolizumab vs. Other Biologic Agents (Ulcerative Colitis and Crohn's Disease)				
NCT02674308 Entyvio (Vedolizumab) Long-term Safety Study: An International Observational Prospective Cohort Study Comparing Vedolizumab to Other Biologic Agents in Patients With Ulcerative Colitis or Crohn's Disease Entyvio PASS; Phase NA	Vedolizumab vs. adalimumab, certolizumab pegol, golimumab, infliximab NA	N = 5,302 7 years	July 2021 (estimated)	Percent of participants with adverse events of special interest
Vedolizumab vs. Infliximab (Ulcerative Colitis)				
NCT03679546 Efficacy of Intravenous Infliximab Versus Vedolizumab After Failure of subcutaneous Anti-TNF in Patients With Ulcerative Colitis (EFFICACI) Phase 4	Vedolizumab 300 mg; infliximab 5 mg/kg Blinded	N = 150 14 weeks	June 2022 (estimated)	Clinical and endoscopic steroid-free remission at week 14

Registration Number Trial Name Phase	Treatment Groups Blinded vs. Open	N Enrolled Treatment Duration	Study Completion Date	Primary Outcome(s)
Guselkumab vs. Ustekinumab (Crohn's Disease)				
NCT03466411 A Phase 2/3, Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants With Moderately to Severely Active Crohn's Disease (GALAXI) Phase 2/3	Guselkumab (5 doses); ustekinumab; placebo Blinded	N = 2,000 (estimated) 12 weeks	October 2024 (estimated)	Phase 2: Change from baseline in the CDAI score at week 12. Phase 3: Clinical remission at week 12.
Risankizumab vs. Placebo (Crohn's Disease)				
NCT03105102 A Study of the Efficacy and Safety of Risankizumab in Subjects With Crohn's Disease Who Responded to Induction Treatment in M16-006 or M15-991 or Completed M15-989 Phase 3	Risankizumab (SC and IV); placebo Blinded	N = 912 52 weeks	June 2026 (estimated)	Endoscopic response at week 52; clinical remission at week 52
NCT03104413 A Study to Assess the Efficacy and Safety of Risankizumab in Subjects With Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment Phase 3	Risankizumab (SC and IV); placebo Blinded	N = 579 12 weeks	March 2021 (estimated)	Endoscopic response at week 12; clinical remission at week 12
Risankizumab vs. Placebo (Ulcerative Colitis)				
NCT03398135 A Study to Assess the Efficacy and Safety of Risankizumab in Subjects With Ulcerative Colitis Who Responded to Induction Treatment in M16-067 or M16-065 Phase 3	Risankizumab (SC and IV); placebo Blinded	N = 760 52 weeks	June 2024 (estimated)	Clinical remission at week 52
NCT03398148 A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Evaluate the Efficacy and Safety of Risankizumab in Subjects With Moderately to Severely Active Ulcerative Colitis Who Have Failed Prior Biologic Therapy Phase 2/3	Risankizumab (SC and IV); placebo Blinded	N = 720 12 weeks	August 2022 (estimated)	Clinical remission at week 12

Registration Number Trial Name Phase	Treatment Groups Blinded vs. Open	N Enrolled Treatment Duration	Study Completion Date	Primary Outcome(s)
Upadacitinib vs. Placebo (Crohn's Disease)				
NCT03345836 A Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects With Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or Are Intolerant to Biologic Therapy Phase 3	Upadacitinib; placebo Open and blinded	N = 645 12 weeks	June 2021 (estimated)	Clinical remission at week 12; endoscopic remission at week 12
NCT03345849 A Study of the Efficacy and Safety of Upadacitnib (ABT-494) in Subjects With Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or Are Intolerant to Conventional and/or Biologic Therapies Phase 3	Upadacitinib; placebo Blinded	N = 501 12 weeks	September 2021 (estimated)	Endoscopic response at week 12; clinical remission at week 12
NCT02782663 A Study to Evaluate the Long-Term Efficacy, Safety, and Tolerability of Repeated Administration of Upadacitinib (ABT-494) in Subjects With Crohn's Disease Phase 2	Upadacitinib; placebo Open	N = 107 96 months	September 2025 (estimated)	Remission at month 96
Upadacitinib vs. Placebo (Ulcerative Colitis)				
NCT03006068 A Study to Evaluate the Long-Term Safety and Efficacy of Upadacitinib (ABT-494) in Subjects With Ulcerative Colitis (UC) Phase 3	Upadacitinib (multiple doses); placebo Blinded	N = 950 288 weeks	August 2024 (estimated)	Treatment-emergent adverse events up to week 288
NCT02819635 A Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis (UC) Phase 3	Upadacitinib (multiple doses); placebo Blinded	N = 844 52 weeks	February 2022 (estimated)	Clinical remission at week 8; clinical remission at week 44 or 52

Abbreviations. CDAI: Crohn's Disease Activity Index; IV: intravenous; NA: not applicable; NCT: U.S. National Clinical Trial number; SC: subcutaneous; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha.

Discussion

Overall, limited evidence exists for the comparative effectiveness and harms of TIM agents for the treatment of Crohn's disease. The evidence was previously rated as very low quality for the comparative effectiveness of adalimumab and infliximab, and we did not identify any new RCTs evaluating comparative effectiveness of these agents or any other comparisons in this update. We identified 1 new cohort study evaluating the comparative harms of adalimumab and infliximab, but study limitations, indirectness, and imprecision prevent the comparative harms body of evidence from rising above very low quality. We identified no new cohort studies comparing harms between adalimumab and other agents (infliximab, etanercept, certolizumab pegol); thus, the quality of evidence on comparative harms for these agents remains very low. We identified 1 new pipeline TIM agent (PF-04236921), which at the higher dosage evaluated was more effective than placebo on measures of clinical improvement and remission (moderate and low quality of evidence, respectively), with no statistically significant differences in harms (moderate to low quality of evidence).

We identified 1 new RCT for this update for the comparative effectiveness and harms of TIMs for ulcerative colitis.[14] Authors of this study reported higher efficacy and no statistically significant difference in harms for vedolizumab compared to adalimumab; we assessed this study as moderate quality of evidence for effectiveness outcomes and low quality of evidence for harm outcomes. In the previous update, only comparative harms from observational studies were available for the ulcerative colitis population. We identified 1 additional observational study comparing infliximab with adalimumab for this update, but as with Crohn's disease, the quality of evidence on comparative harms among TIMs for ulcerative colitis remains as very low.

Data from Network Meta-Analyses

We identified 2 relevant network meta-analyses (NMA) that provided indirect comparisons of TIM agents; both focused on patients with moderate-to-severe ulcerative colitis.[31,32] The review by Trigo-Vicente et al.[32] did not include the literature search dates, whereas the review by Bonovas et al.[31] searched literature through August 2017. Trigo-Vicente et al.[32] included 14 publications describing 18 RCTs whereas Bonovas et al.[31] included 13 publications describing 19 RCTs. In addition to studies evaluating TIMs of relevance to this update, these analyses also include placebo-controlled trials and trials evaluating agents not approved or currently in the approval pipeline in the U.S. The rest of this section describes the findings from each of these NMAs.

Bonovas et al.[31] analyzed 19 placebo-controlled RCTs of induction or maintenance therapy of the following agents: tofacitinib (4 RCTs), adalimumab (4 RCTs), golimumab (5 RCTs), infliximab (4 RCTs), and vedolizumab (2 RCTs). Patients in the included trials were not previously exposed to TNF-α inhibitors. All treatments evaluated were more effective than placebo based on the direct evidence. Table E1 (Appendix E) summarizes the detailed results of indirect comparisons for the various outcomes. Patients taking infliximab achieved significantly better results than those taking adalimumab and golimumab for induction of clinical response and mucosal healing; patients taking infliximab achieved significantly better results than adalimumab for induction of clinical remission.[31] For safety, golimumab use was associated with more than a two-fold increase in SAEs compared to vedolizumab (odds ratio [OR] 2.15; 95% CI, 1.01 to 4.59).[31]

Bonovas et al. did not identify any other significant indirect treatment comparisons for safety outcomes.

Trigo-Vicente et al.[32] analyzed 18 RCTs; the Bonovas et al.[31] NMA included all but 3 of these RCTs. The 3 RCTs only incorporated in the Trigo-Vincente et al. NMA include an active-control trial comparing adalimumab to infliximab, and 2 placebo-controlled trials of etrolizumab and ozanimod. The agents of relevance to this current update included in the Trigo-Vicente et al. NMA were adalimumab, golimumab, infliximab, tofacitinib, and vedolizumab.[23] All agents were more effective than placebo for induction of clinical response. In indirect treatment comparisons, infliximab was significantly more effective than adalimumab for induction of clinical response (OR, 2.10; 95% CI, 1.33 to 3.27) and induction of clinical remission (OR, 2.35; 95% CI, 1.35 to 4.14). Infliximab was also more effective than adalimumab (OR, 2.01; 95% CI, 1.28 to 3.16) and golimumab (OR, 1.67; 95% CI, 1.04 to 2.07) for mucosal healing.[23] For maintenance therapy, all treatments were more effective than placebo. In indirect treatment comparisons for maintenance of clinical remission, tofacitinib was significantly more effective than adalimumab and both dosages of golimumab (50 mg and 100 mg). Tofacitinib and vedolizumab were significantly better than adalimumab and both dosages of golimumab for maintenance of mucosal healing.[23] For safety outcomes, tofacitinib, both dosages of golimumab, and vedolizumab had significantly higher rates of infection compared to placebo, but the authors found no significant indirect treatment comparisons between any of the agents for infections or SAE.[23]

Limitations of the Evidence

Few RCTs that evaluate the comparative effectiveness and harms of TIM agents for the treatment of Crohn's disease or ulcerative colitis exist. The RCTs we identified were likely not statistically powered to evaluate AEs. Drug manufacturers sponsored all the included RCTs. Although the extent to which the manufacturer's involvement influenced study execution or reporting is not definitively known, findings from a recent Cochrane systematic review suggest that industry sponsorship is associated with more favorable results than sponsorship by other sources.[33] Nearly all of the cohort studies that we included used administrative or claims data to evaluate harms, and the validity of this approach for evaluating harms is uncertain.

Limitations of this Review

This review has several limitations. First, we did not include RCTs shorter than 12 weeks duration, cohort studies with fewer than 1,000 participants, or studies published in languages other than English. We included only studies published in the peer-reviewed literature; we did not use data presented in press releases or conference abstracts. This review represents a cumulative synthesis of the evidence; thus, studies included in the prior DERP review on this topic were carried forward into this update if they continued to meet eligibility criteria. However, data from these studies were not rechecked against the original sources for accuracy. Further, we did not reevaluate the methodological study quality for the previously included studies except for RCTs that were previously assessed as good quality. We reassessed these good-quality RCTs to determine the influence of manufacturer involvement on study design and execution for consistency with current Center methodology. Lastly, the previous report used a modified GRADE approach whereby the lowest quality rating was termed *insufficient*; we

converted all previous insufficient strength of evidence ratings to *very low* for consistency with current GRADE methodology.

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Appendix A. Methods

Search Strategy

We searched Drug Effectiveness Review Project (DERP) clinical evidence sources to identify systematic reviews (with and without meta-analyses), technology assessments, randomized controlled trials (RCTs), and cohort studies (for harms) using terms for the conditions *(Crohn's disease, ulcerative colitis) a*nd the interventions *(adalimumab, adalimumab-adaz, adalimumab-adbm, adalimumab-atto, certolizumab pegol, golimumab, infliximab, infliximab-abda, infliximab-dyyb, infliximab-qbtx, natalizumab, ustekinumab, vedolizumab, risankizumab, upadacitinib, peficitinib, PF-04236921, and all brand-name equivalents)* and study designs. We limited searches of evidence sources to citations published from January 1, 2017 through August 20, 2019. We conducted active surveillance of both published literature and ongoing studies through December 31, 2019.

The following DERP evidence sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
  - Evidence-based Practice Centers (EPC) Reports
  - Effective Health Care (EHC) Program
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- National Institute for Health and Care Excellence (NICE)
- Ovid MEDLINE
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Embase
- Clinical Trials.gov
- ISRCTN

Ovid MEDLINE Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to August 20, 2019

#	Searches
1	Crohn Disease/
2	Colitis, Ulcerative/
3	crohn* disease.ti,ab,kf.
4	((ulcerative or gravis) adj1 colitis).ti,ab,kf.
5	or/1-4
6	Biological Products/
7	(biologic therap* or biologics).ti,ab.
8	Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
9	((tumor necrosis factor alpha or TNF-alpha) adj2 (inhibitor? or anti or block* or antagonist?)).ti,ab.
10	exp Receptors, Interleukin/ai [Antagonists & Inhibitors]
11	(interleukin adj2 (inhibitor? or anti or block* or antagonist?)).ti,ab.
12	exp Janus Kinases/ai [Antagonists & Inhibitors]
13	((janus kinase or JAK?) adj2 (inhibitor? or anti or block* or antagonist?)).ti,ab.
14	antibodies, monoclonal/ or antibodies, monoclonal, humanized/
15	monoclonal antibod*.ti,ab.
16	Adalimumab/
17	(adalimumab or Humira or Amjevita or Hyrimoz or Cyltezo).mp.
18	Certolizumab Pegol/

#	Searches
19	(Certolizumab or Cimzia).mp.
20	(golimumab or simponi or CNTO148 or "CNTO 148").af.
21	Infliximab/
22	(infliximab or Remicade or Renflexis or Inflectra or Ixifi).mp.
23	Ustekinumab/
24	(Ustekinumab or Stelara).mp.
25	Natalizumab/
26	(Natalizumab or Tysabri).mp.
27	(Vedolizumab or Entyvio or "LDP 02" or LDP02 or "MLN 02" or MLN02).af.
28	or/6-27
29	limit 28 to yr = "2017 -Current"
30	(Upadacitinib or ABT494 or "ABT 494").af.
31	(Risankizumab or Skyrizi or "BI 655066" or BI655066 or "ABBV 066" or ABBV066).af.
32	(Peficitinib or Smyraf or ASP-015K or ASP015K or JNJ-54781532 or JNJ54781532).af.
33	(PF-04236921 or PF04236921).af.
34	or/29-33
35	5 and 34
36	exp animals/ not humans/
37	35 not 36
38	exp age groups/ not exp adult/
39	37 not 38
40	Systematic Review.pt.
41	(systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)
42	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X).is.
43	meta-analysis.pt. or Network Meta-Analysis/ or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).tw,hw.
44	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)
45	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).tw,hw. or (quantitativ$ adj5 synthesis$).tw,hw.
46	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.
47	or/40-46
48	47 not (case report/ or letter.pt.)
49	48 and 39
50	randomized controlled trial.pt. or random*.mp. or placebo.mp.
51	50 and 39
52	exp Antirheumatic Agents/ae [Adverse Effects]
53	exp Antibodies, Monoclonal/ae [Adverse Effects]
54	Biological Products/ae [Adverse Effects]
55	"Drug-Related Side Effects and Adverse Reactions"/
56	Long-Term Adverse Effects/
57	((adverse or dangerous or harmful or indirect or injurious or secondary or side or undesirable) adj2 (effect* or event* or consequence* or impact* or outcome* or reaction*)).ti,ab.
58	(drug adj (survival or retention or longevity or adherence)).ti,ab.
59	(harms or safety or complication?).ti.

#	Searches
60	(toxicity or ((injection site or infusion) adj reaction?) or mortality or infection? or tuberculosis or herpes or malignan* or skin cancer? or heart failure or heart disease? or cardiovascular risk or lung disease? or ((gastrointestinal or gastrointestinal) adj perforation?)).ti.
61	or/52-60
62	61 and 39
63	49 or 51 or 62

Cochrane Library Search Strategy

Cochrane Library (Wiley) – 21 August 2019

ID	Search
#1	[mh ^"Crohn Disease"]
#2	[mh ^"Colitis, Ulcerative"]
#3	((ulcerative or gravis) NEXT colitis):ti,ab,kw
#4	(or #1-#3)
#5	[mh ^"Adalimumab"]
#6	(adalimumab or Humira or Amjevita or Hyrimoz or Cyltezo):ti,ab,kw
#7	[mh ^"Certolizumab Pegol"]
#8	(Certolizumab or Cimzia):ti,ab,kw
#9	(golimumab or simponi or CNTO148 or "CNTO 148"):ti,ab,kw
#10	[mh ^"Infliximab"]
#11	(infliximab or Remicade or Renflexis or Inflectra or Ixifi):ti,ab,kw
#12	[mh ^"Ustekinumab"]
#13	(Ustekinumab or Stelara):ti,ab,kw
#14	[mh ^"Natalizumab"]
#15	(Natalizumab or Tysabri):ti,ab,kw
#16	(Vedolizumab or Entyvio or "LDP 02" or LDP02 or "MLN 02" or MLN02):ti,ab,kw
#17	(or #5-#16) with Cochrane Library publication date Between Oct 2017 and Aug 2019
#18	(Upadacitinib or ABT494 or "ABT 494"):ti,ab,kw
#19	(Risankizumab or Skyrizi or "BI 655066" or BI655066 or "ABBV 066" or ABBV066):ti,ab,kw
#20	(Peficitinib or Smyraf or ASP-015K or ASP015K or JNJ-54781532 or JNJ54781532):ti,ab,kw
#21	(PF-04236921 or PF04236921):ti,ab,kw
#22	(or #17-#21)
#23	#4 and #22
#24	[mh "age groups"] not [mh adult]
#25	#23 not #24
#26	(clinicaltrials or trialsearch or ANZCTR or ensaiosclinicos or chictr or cris or ctri or registroclinico or clinicaltrialsregister or DRKS or IRCT or rctportal or JapicCTI or JMACCT or jRCT or UMIN or trialregister or PACTR or REPEC or SLCTR):so
#27	#25 not #26

Embase Search Strategy

Embase.com (Elsevier) – 21 August 2019

No.	Query
#1	'crohn disease'/exp
#2	'ulcerative colitis'/exp
#3	'crohn* disease':ti,ab
#4	((ulcerative OR gravis) NEAR/1 colitis):ti,ab
#5	#1 OR #2 OR #3 OR #4

No.	Query
#6	'adalimumab'/exp/mj
#7	adalimumab:ti,ab OR humira:ti,ab OR amjevita:ti,ab OR hyrimoz:ti,ab OR cyltezo:ti,ab
#8	'certolizumab pegol'/exp/mj
#9	certolizumab:ti,ab OR cimzia:ti,ab
#10	'golimumab'/exp/mj
#11	golimumab:ti,ab OR simponi:ti,ab OR cnto148:ti,ab OR 'cnto 148':ti,ab
#12	'infliximab'/exp/mj
#13	infliximab:ti,ab OR remicade:ti,ab OR renflexis:ti,ab OR inflectra:ti,ab OR ixifi:ti,ab
#14	'ustekinumab'/exp/mj
#15	ustekinumab:ti,ab OR stelara:ti,ab
#16	'natalizumab'/exp/mj
#17	natalizumab:ti,ab OR tysabri:ti,ab
#18	'vedolizumab'/exp/mj
#19	vedolizumab:ti,ab OR entyvio:ti,ab OR 'ldp 02':ti,ab OR ldp02:ti,ab OR 'mln 02':ti,ab OR mln02:ti,ab
#20	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) AND [2017-2019]/py
#21	'upadacitinib'/exp/mj
#22	upadacitinib:ti,ab OR abt494:ti,ab OR 'abt 494':ti,ab
#23	'risankizumab'/exp/mj
#24	risankizumab:ti,ab OR skyrizi:ti,ab OR 'bi 655066':ti,ab OR bi655066:ti,ab OR 'abbv 066':ti,ab OR abbv066:ti,ab
#25	'peficitinib'/exp
#26	peficitinib:ti,ab OR smyraf:ti,ab OR 'asp 015k':ti,ab OR asp015k:ti,ab OR 'jnj 54781532':ti,ab OR jnj54781532:ti,ab
#27	'pf 04236921' OR pf04236921
#28	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#29	#5 AND #28
#30	'animal'/exp NOT 'human'/exp
#31	#29 NOT #30
#32	'groups by age'/exp NOT 'adult'/exp
#33	#31 NOT #32
#34	'systematic review'/exp OR 'meta-analysis'/exp
#35	(((systematic OR 'state of the art' OR scoping OR umbrella) NEXT/1 (review* OR overview* OR assessment*)):ti,ab) OR 'review* of reviews':ti,ab OR 'meta analy*':ti,ab OR metaanaly*:ti,ab OR (((systematic OR evidence) NEAR/1 assess*):ti,ab) OR 'research evidence':ti,ab OR metasynthe*:ti,ab OR 'meta synthe*':ti,ab
#36	#34 OR #35
#37	#33 AND #36
#38	'randomized controlled trial'/exp OR random*:ti,ab OR placebo:ti,ab
#39	#33 AND #38
#40	'adalimumab'/exp/dd_ae OR 'certolizumab pegol'/exp/dd_ae OR 'golimumab'/exp/dd_ae OR 'infliximab'/exp/dd_ae OR 'ustekinumab'/exp/dd_ae OR 'natalizumab'/exp/dd_ae OR 'vedolizumab'/exp/dd_ae OR 'upadacitinib'/exp/dd_ae OR 'risankizumab'/exp/dd_ae OR 'peficitinib'/dd_ae
#41	'adverse drug reaction'/de
#42	((adverse OR dangerous OR harmful OR indirect OR injurious OR secondary OR side OR undesirable) NEAR/2 (effect* OR event* OR consequence* OR impact* OR outcome* OR reaction*)):ti,ab
#43	(drug NEXT/1 (survival OR retention OR longevity OR adherence)):ti,ab

No.	Query
#44	harms:ti OR safety:ti OR complication$:ti
#45	toxicity:ti OR ((('injection site' OR infusion) NEXT/1 reaction$):ti) OR mortality:ti OR infection$:ti OR tuberculosis:ti OR herpes:ti OR malignan*:ti OR "skin cancer$":ti OR 'heart failure':ti OR "heart disease$":ti OR 'cardiovascular risk':ti OR "lung disease$":ti OR (((gastrointestinal OR 'gastro intestinal') NEXT/1 perforation$):ti)
#46	#40 OR #41 OR #42 OR #43 OR #44 OR #45
#47	#33 AND #46
#48	#37 OR #39 OR #47
#49	#48 NOT 'conference abstract'/it

Ongoing Studies

We searched the following DERP sources for ongoing studies. We selected search terms depending on the information source (see below):

ClinicalTrials.gov – 21 August 2019

Search
crohn OR crohn's OR crohns OR colitis | adalimumab OR Humira OR Amjevita OR Hyrimoz OR Cyltezo OR Certolizumab OR Cimzia OR golimumab OR simponi OR CNTO148 OR "CNTO 148" OR infliximab OR Remicade OR Renflexis OR Inflectra OR Ixifi OR Ustekinumab OR Stelara OR Natalizumab OR Tysabri | Adult, Older Adult | Last update posted from 11/01/2017 to 08/21/2019
crohn OR crohn's OR crohns OR colitis | Vedolizumab OR Entyvio OR "LDP 02" OR LDP02 OR "MLN 02" OR MLN02 OR Upadacitinib OR ABT494 OR "ABT 494" OR Risankizumab OR Skyrizi OR "BI 655066" OR BI655066 OR "ABBV 066" OR ABBV066 | Adult, Older Adult | Last update posted from 11/01/2017 to 08/21/2019
crohn OR crohn's OR crohns OR colitis | Peficitinib OR Smyraf OR ASP-015K OR ASP015K OR JNJ-54781532 OR JNJ54781532 | Adult, Older Adult | Last update posted from 11/01/2017 to 08/21/2019
Total (before internal deduplication) 221
Total (after deduplication) 208

ISRCTN Registry – 13 August 2019

Search
adalimumab OR Humira OR Amjevita OR Hyrimoz OR Cyltezo OR Certolizumab OR Cimzia OR golimumab OR simponi OR CNTO148 OR "CNTO 148" OR infliximab OR Remicade OR Renflexis OR Inflectra OR Ixifi OR Ustekinumab OR Stelara OR Natalizumab OR Tysabri | filter within Condition: Crohn OR crohn's OR crohns OR colitis | filter Participant age range: Adult | filter Date applied: from: 01/11/2017 | filter Date applied: to: 21/08/2019
Vedolizumab OR Entyvio OR "LDP 02" OR LDP02 OR "MLN 02" OR MLN02 OR Upadacitinib OR ABT494 OR "ABT 494" OR Risankizumab OR Skyrizi OR "BI 655066" OR BI655066 OR "ABBV 066" OR ABBV066 | filter within Condition: Crohn OR crohn's OR crohns OR colitis | filter Participant age range: Adult | filter Date applied: from: 01/11/2017 | filter Date applied: to: 21/08/2019
Peficitinib OR Smyraf OR ASP-015K OR ASP015K OR JNJ-54781532 OR JNJ54781532 | filter within Condition: Crohn OR crohn's OR crohns OR colitis | filter Participant age range: Adult | filter Date applied: from: 01/11/2017 | filter Date applied: to: 21/08/2019
Total (before internal deduplication) 99
Total (after deduplication) 97

Inclusion Criteria

Population

- Adults with Crohn's disease
- Adults with ulcerative colitis

Interventions

- TIMs and respective biosimilars that the FDA has approved for the treatment of Crohn's disease or ulcerative colitis and select pipeline drugs likely to be approved soon

Comparators

- For FDA-approved drugs: another listed TIM intervention (head-to-head comparison)
- For pipeline drugs: any listed TIM, standard of care, placebo

Outcomes

- Health outcomes
  - Quality of life
  - Functional capacity
  - Productivity, ability to sustain employment
  - Clinical improvement
  - Disease remission
  - Pain
  - Reduction in disease-related hospitalizations
  - Reduction in disease-specific mortality
  - Rebound/flare
  - Steroid withdrawal
- Harms
  - Overall adverse events (AEs)
  - Withdrawals due to AEs
  - Serious adverse events
  - Specific AE (e.g., lymphoma, all malignancies, serious infectious diseases, herpes zoster, opportunistic infections, congestive heart failure)
  - Mortality

Study Designs

- RCTs with ≥ 12-week study duration
- Retrospective and prospective cohort studies comparing an intervention type to another for outcomes on harms
  - > 12-week study duration
  - Minimum total sample size of 1,000

Exclusion Criteria

We excluded studies if they were not published in English. We also excluded conference abstracts and data reported in press releases.

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases where we disagreed about eligibility, we resolved the disagreement through discussion. We repeated this method for full-text review of documents that we could not exclude by title and abstract screening.

Data Abstraction

One experienced researcher abstracted and entered data from eligible studies in a standardized way using DistillerSR. A second experienced researcher reviewed all the data entered. We resolved discrepancies through discussion. We pulled forward data from studies included in the prior report directly into tables in the update report.

Quality Assessment

Methodological Quality of Included Studies

We assessed the methodological quality of the included RCTs and cohort studies using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[6-10] Two experienced researchers independently rated all included studies. In cases where we disagreed about the methodological quality of a study, we resolved the disagreement through discussion.

Randomized Controlled Trials

Good-quality RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality RCTs also have low potential for bias from conflicts of interest and funding source(s). Fair-quality RCTs have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. Poor-quality RCTs have clear flaws that could introduce significant bias.

Cohort Studies

Good-quality cohort studies include a sample that is representative of the source population, have low loss to follow-up, and measure and consider relevant confounding factors. Good-quality cohort studies also list their funding source(s) and have a low potential of bias from conflicts of interest. Fair-quality cohort studies might not have measured all relevant confounding factors or adjusted for them in statistical analyses, have loss to follow-up that could bias findings, consist of a sample that is not representative of the source population, or have potential conflicts of interest that are not addressed. Poor-quality cohort studies have a clear, high risk of bias that would affect findings.

Quality of Evidence Assessment

Overall Quality of Evidence

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[11,12] Two independent experienced researchers assigned

ratings, with disagreements resolved through discussion. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

Table B1. Evidence Table for RCTs of TIMs for Crohn's Disease or Ulcerative Colitis (Study and Population Characteristics)

Author, Year Country Trial Name Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
Van Assche et al.,[20] 2011 Belgium None Fair	Luminal Crohn's patients treated with scheduled infliximab maintenance therapy started at least 6 months before without episodic use during that time period; a durable complete clinical response with stable infliximab dosing intervals of at least 6 weeks for the last 6 months was required. Patients with a draining abdominal enterocutaneous fistula, with a medical condition or laboratory tests precluding further anti-TNF-α therapy, with previous exposure to adalimumab, receiving infliximab doses > 5 mg/kg intravenously and those with an imminent need for surgery were excluded.	Age: 18 or more Gender: NR Ethnicity: NR	Patients with complete loss of response or intolerance were able to cross over to the alternative treatment group.	Authors independently did the following: design and conduct of the trial, data analysis, and manuscript writing. Abbott GMBH, Ludwigshafen, Germany, analyzed adalimumab serum levels. Abbott Belgium provided adalimumab for the patients in this trial.
Tursi et al.,[16] 2014 Italy None Poor	20 consecutive patients with Crohn's disease who were at high risk of postoperative recurrence after undergoing curative ileocolonic resection. Patients were considered at high risk for postoperative recurrence if they had 2 or more risk factors: young age at diagnosis (≤ 30 years), penetrating disease, active smoking, perianal disease at diagnosis, previous surgery and < 3 years from previous surgery.	Age: median age 32.5 years, range 20-39 years Gender: 9 males, 11 females Ethnicity: NR	Exclusion criteria included active perianal disease, presence of stoma, adverse events during previous therapy with infliximab or azathioprine, age > 70 years, surgical complications, active infectious diseases, history of cancer, renal, cardiac or hepatic failure, history of acute or chronic pancreatitis, severe leucopenia (white blood cell count < 3,000 µu/mL, lymphocyte count < 1,000 µu/mL) and pregnancy.	Funding: NR

Author, Year Country Trial Name Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
			9 patients received infliximab before surgery.	
Danese et al.,[15] 2017 Multicountry (Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, New Zealand, Romania, Switzerland, UK, US) ANDANTE I and II Fair	Inclusion criteria included adults aged 18-75 years with moderate-to-severe Crohn's disease (CDAI score 220-450) and failed or are intolerant to ≥ 1 anti-TNF-α; adults with C-reactive protein ≥ 5.0 mg/L; and ulceration demonstrated by colonoscopy performed within 8 weeks of study. Permitted treatments include mesalamine, immunosuppressive (azathioprine, 6-mercaptopurine or methotrexate) at stable dosages for > 6 weeks, and/or oral prednisone ≤ 20 mg/day or oral budesonide ≤ 6 mg/day. Corticosteroid dosage tapering was permitted following clinical remission (CDAI score < 150) or in response to adverse events. The regular use of nonsteroidal anti-inflammatory drugs was not permitted; however, occasional use of ibuprofen ≤ 800 mg on any day was allowed during the study. Exclusion criteria included prior exposure to anti-interleukin-6 biologic agent, natalizumab, vedolizumab or an unapproved biologic agent (within previous 12 months); any investigational procedure, drug or live vaccine within 4 weeks of baseline; diverticulitis or active fistulae or abscess.	Age criteria: 18-75 years, mean in each group ranged from 38.4 to 42.2. Gender: 141 females (57.1%) Ethnicity: NR	Mean CDAI Score (SD): • Placebo: 320.7 (64.2) • 10 mg: 319.9 (61.9) • 50 mg: 296.7 (63.3) • 200 mg: 337.4 (73.4) Current use of immuno-suppressive therapy, n (%): • Azathioprine: 38 (15.4%) • 6-Mercaptopurine: 8 (3.2%) • Methotrexate: 21 (8.5%) • Corticosteroids: 100 (40.5%) • No immunosuppressive therapy: 180 (72.9%)	Pfizer

Author, Year Country Trial Name Study Quality	Population	Age Gender Ethnicity	Other Population Characteristics	Funding
Sands et al.[14], 2019 US and 33 other countries VARSITY Fair	Adults aged 18-85 years with moderate-to-severe ulcerative colitis determined by a total Mayo score of 6 to 12 with a subscore of at least 2 on the endoscopic component; at least 15 cm colonic involvement; a diagnosis of ulcerative colitis at least 3 months before screening. Patients who discontinue treatment with a TNF inhibitor (except adalimumab) for any reason other than safety were eligible with enrollment capped for this group at 25%. All patients had not previously received vedolizumab. Of patients using oral corticosteroid the dosing must be stable at least 2 weeks before the first dose of trial drug (dosing was stable for 6 weeks after which the dosing was tapered; patients that did not tolerate tapering were discontinued).	Age criteria: 18-85 years; mean age in years (SD): • Adalimumab: 40.5 (13.4) • Vedolizumab: 40.8 (13.7) Gender: N (%): • Adalimumab: 170 females (44.0)[a] • Vedolizumab: 151 females (39.2)[a] Ethnicity: N (%) • Adalimumab: 341 Caucasian (88.3%) • Vedolizumab: 345 Caucasian (89.6%)	Mean (SD) duration of ulcerative colitis: • Adalimumab: 6.4 (6.0) • Vedolizumab: 7.3 (7.2) Mean (SD) Mayo score: • Adalimumab: 8.7 (1.5) • Vedolizumab: 8.7 (1.6) N (%) concomitant use of corticosteroids only: • Adalimumab: 140 (36.3) • Vedolizumab: 139 (36.1) N (%) concomitant use of immunomodulators only: • Adalimumab: 100 (25.9) • Vedolizumab: 101 (26.2)	Takeda

Note. [a]Indicates a calculated value. Abbreviations. CDAI: Crohn's Disease Activity Index; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; TIM: targeted immune modulators; TNF: tumor necrosis factor; UK: United Kingdom; US: United States.

Table B2. Evidence Table for RCTs of TIMs for Crohn's Disease or Ulcerative Colitis (Intervention and Results)

Author, Year Country Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
Van Assche et al.,[20] 2011 Belgium None Fair	Patients were randomized to continue infliximab 5 mg/kg intravenously at the same interval for 56 weeks or to switch to adalimumab. Patients in the adalimumab group received 80 mg SC at inclusion and 40 mg SC every other week for 54 weeks.	73 • 36 adalimumab • 37 infliximab	The median CDAI at time of early termination in the adalimumab group was 184 (IQR 44-235) compared to 78 (IQR 35-134; *P* = .10) at baseline. Median IBDQ values at baseline and at week 56 were comparable in both groups and the medians stayed well in the range compatible with disease remission throughout the trial • Adalimumab ○ week 0: 197 (IQR 181-212), ○ week 54: 193 (IQR 160-214) • Infliximab ○ week 0: 191 (IQR 172-203) ○ week 54: 188 (IQR 170-204)	All serious AE occurred in 5 patients originally assigned to the adalimumab group (*P* < .05 vs infliximab group); two patients returned to infliximab when the AE occurred.	Upper respiratory tract infections, fatigue, skin lesions and injection site reactions were the most frequently occurring events. Injection site reactions were all mild and occurred in 8 of 36 patients in the adalimumab group and 1 patient had an infusion reaction in the infliximab group (*P* = .01)
Tursi et al.,[16] 2014 Italy None Poor	Patients were randomized to receive infliximab (5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks) or adalimumab (160 mg SC, followed by 80 mg 2 weeks later, and then 40 mg every 2 weeks) for 1 year. Treatment started within 4-6 weeks after surgery. All patients also received oral metronidazole (500-mg	20	Endoscopic, histological, and clinical recurrence after 12 months of therapy in the two groups was assessed. At the end of the follow-up, 2 (20%) patients treated with infliximab had endoscopic recurrence compared to 1 (10%) patient in the adalimumab group (*P* = 1.0). According to the Geboes scale for assessment of histological disease activity, at the end of the study 3 of 10 (30%) patients treated with infliximab had moderate histological activity (score	None investigated	None investigated

Author, Year Country Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
	bid) for 2 weeks after surgery. No other CD-related drugs were admitted during the study.		≥ 4.1), compared to 2 of 10 (20%) in the adalimumab group (*P* = 1.0). No significant difference in clinical recurrence rates: 1 of 10 (10%) infliximab patients treated and 1 of 10 (10%) adalimumab patients (*P* = 1.0). No significant difference in the median C-reactive protein level in the two groups: 2.01 mg/L (mean range 0.7-3.4) in patients treated with infliximab compared to 1.8 mg/L (mean range 0.8-2.4) in the adalimumab group (*P* = .86).		
Danese et al.,[15] 2017 Multicountry (Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, New Zealand, Romania, Switzerland, UK, US)	Patients were randomized 1:1:1:1 to receive placebo or PF-04236921 10, 50, or 200 mg SC, on days 1 and 28. After the induction period, patients entered either a 28-week follow-up period or the 48-week open label extension study. Only the data associated with the double-blind controlled induction period is included in this report.	N Total = 247 • Placebo: 70 randomized, 69 analyzed • PF-04236921 10 mg: 68 randomized, 67 analyzed • PF-04236921 50 mg: 71 randomized and analyzed • PF-04236921 200 mg: 40 randomized and analyzed (note: this	CDAI-70 (% achieving a 70-point reduction) • Week 8 ○ Placebo: 30.6% ○ 10 mg: 35.0% (*P* > .05 vs. placebo) ○ 50 mg: 49.3% (*P* < .05 vs. placebo) • Week 12 ○ Placebo: 28.6% ○ 10 mg: 35.2% (*P* > .05 vs. placebo) ○ 50 mg: 47.4% (*P* < .05 vs. placebo) Significant differences between 50 mg and placebo also observed at weeks 4, 6, and 10. No significant differences between 10 mg and placebo at any time point. CDAI -100 (% achieving a 100-point reduction) at week 12: • Placebo: only reported on a figure • 10 mg: only reported on a figure	N (%) incidence of any AEs: • Placebo: 63 (91.3) • 10 mg: 60 (89.6); RR 0.98[a]; 95% CI, 0.88 to 1.10 • 50 mg: 58 (81.7); RR 0.89[a]; 95% CI, 0.78 to 1.02 • 200 mg: 33 (82.5) N (%) incidence of severe AEs: • Placebo: 5 (7.2) • 10 mg: 12 (17.9); RR 2.5; 95% CI[a], 0.92 to 6.6 • 50 mg: 12 (16.9); RR 2.33; 95% CI[a], 0.87 to 6.3 • 200 mg: 5 (12.5)	N (%) incidence of injection site reaction: • Placebo: 4 (5.8) • 10 mg: 2 (3.0); RR 0.51[a]; 95% CI, 0.10 to 2.7 • 50 mg: 7 (9.9); RR 1.70[a]; 95% CI, 0.52 to 5.6 • 200 mg: 6 (15.0) The most commonly reported AEs were worsening of CD, abdominal pain, headache, and nasopharyngitis.

Author, Year Country Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
ANDANTE I and II Fair		group was stopped early due to fatalities in patients with lupus who were treated with this dosage in a separate trial)	• 50 mg: only reported on a figure Significant difference between 50 mg and placebo at 6 weeks, but not at any other time point. No significant difference between 10 mg and placebo at any time point. CDAI remission rate (CDAI score < 150) at week 12: • Placebo: 10.9% • 10 mg: Only reported on a figure • 50 mg: 27.4% (*P* < .05 vs. placebo) Significant differences between 50 mg and placebo also observed at weeks 2, 4, 6, and 10. No significant differences between 10 mg and placebo at any time point. IBDQ, difference from placebo in mean change from baseline at weeks 4, 8, and 12: • 10 mg: range -13.6 to -4.7 • 50 mg: range -5.7 to -2.2 One-sided *P* > .05 versus placebo for both dosages. EQ-5D, difference from placebo in mean change from baseline at weeks 4, 8 and 12: • 10 mg: -0.013 to 0.18 • 50 mg: 0.011 to 0.043 One-sided *P* > .05 versus placebo for both dosages	N (%) incidence of serious AEs: • Placebo: 9 (13.0) • 10 mg: 7 (10.4); RR 0.80; 95% CI[a], 0.32 to 2.0 • 50 mg: 9 (12.7); RR 0.97; 95% CI[a], 0.41 to 2.3 • 200 mg: 11 (27.5) N (%) incidence of withdrawals due to AE: • Placebo: 7 (10.1) • 10 mg: 6 (9.0); RR 0.88; 95% CI[a], 0.31 to 2.5 • 50 mg: 6 (8.5); RR 0.83; 95% CI[a], 0.30 to 2.4) • 200 mg: 8 (20.0)	

Author, Year Country Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
Sands et al.,[14] 2019 US and 33 other countries VARSITY Fair	Patients randomized 1:1 to vedolizumab (300 mg) or adalimumab (40 mg). Patients randomized to 300 mg vedolizumab given 300 mg on day 1 and at weeks 2, 4, 6, 14, 22, 30, 38, and 46, with SC placebo injections on day 1 (4 injections), week 2 (2 injections), and every 2 weeks following (1 injection). Patients randomized to adalimumab given 160 mg SC in week 1, 80 mg SC in week 2 and 40 mg SC every 2 weeks thereafter alongside intravenous infusions of placebo at day 1 and weeks 2,6 14, 22, 30, 38, 46.	N overall: 769 • Adalimumab: 40 mg, 386 randomized and analyzed • Vedolizumab: 300 mg, 383 randomized and analyzed	N (%) with clinical remission at 52 weeks: • Adalimumab: 87 (22.5) • Vedolizumab: 120 (31.3) • aARD 8.8%; 95% CI, 2.5% to 15.0% N (%) with endoscopic improvement at 52 weeks: • Adalimumab: 107 (27.7) • Vedolizumab: 152 (39.7) • aARD 11.9%; 95% CI, 5.3% to 18.5% N (%) with corticosteroid-free clinical remission (of those on steroids at baseline): • Adalimumab: 26 (21. 8) • Vedolizumab: 14 (12.6) • aARD 9.3%; 95% CI, 18.9% to 0.4% % with > 16-point improvement on 52.0% of the patients in the IBDQ at week 52: • Adalimumab: 42.2% • Vedolizumab: 52.0% • ARD 9.7%; 95% CI, 2.7% to 16.7% % with improvement in quality of life (score > 170) on the IBDQ at week 52: • Adalimumab: 40.4% • Vedolizumab: 50.1% • ARD 9.6%; 95% CI, 2.8% to 16.5%	*At week 52* • N(%) with any AE: Adalimumab: 267 (69.2) • Vedolizumab: 240 (62.7) • RR 0.91; 95% CI, 0.82 to 1.00 N(%) with serious AEs: • Adalimumab: 53 (13.7) • Vedolizumab: 42 (11.0) • RR 0.80; 95% CI, 0.55 to 1.17 N (%) with withdrawal due to AE: • Adalimumab: 25 (6.5) • Vedolizumab: 17 (4.4) • RR 0.69; 95% CI, 0.38 to 1.25	*At week 52* N (%) Death • Adalimumab: 0 (0) • Vedolizumab: 1 (0.3) • Not considered to be related to the drug. Incidence of infection/infestations: • Adalimumab: 34.6/100 person-years • Vedolizumab: 23.4/100 person-years • IRR 1.5[a]; 95% CI, 0.89 to 2.5; *P* = .12

Note. [a]Indicates a calculated value. Abbreviations. aARD: adjusted absolute risk difference; AE: adverse events; ARD: absolute risk difference; CD: Crohn's Disease; CDAI: Crohn's Disease Activity Index; CI: confidence interval; EQ-5D: EuroQol 5-dimension assessment instrument; IBDQ: Inflammatory Bowel Disease Questionnaire; IQR: interquartile ratio; IRR: incident rate ratio; RCT: randomized controlled trial; RR: relative risk; SC: subcutaneous; TIM: targeted immune modulators; UK: United Kingdom; US: United States;.

Table B3. Evidence Table for Cohort Studies of Targeted Immune Modulators in Crohn's Disease and Ulcerative Colitis

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame Data Source	Sample Size	Population Characteristics	Harms	Funder
Winthrop et al.,[19] 2013 US Poor	Etanercept, Adalimumab, Infliximab NR NR	January 1, 2000-December 31, 2008 Kaiser Permanente, Northern California	N = 8,418	All Kaiser patients with ≥ 1 clinic visit and ≥ 1 outpatient prescription for etanercept or adalimumab, or ≥ 1 infusion of infliximab for the following indications for anti-TNF therapy: rheumatoid arthritis, psoriasis, psoriatic arthritis, CD, UC, and ankylosing spondylitis. Most (61%) were patients carrying diagnostic codes for rheumatoid arthritis, 64% were women and 61% were White non-Hispanic.	Crude incidence rate (95% CI) per 100,000 patient-years for tuberculosis • Etanercept: 17 (0 to 41) • Infliximab: 83 (10 to 156) • Adalimumab: 91 (19 to 267) • IRR 4.9; 95% CI, 3.0 to 8.5[a] (infliximab vs. etanercept) • IRR 5.6; 95% CI, 3.3 to 9.2[a] (adalimumab vs. etanercept) • IRR 1.1; 95% CI, 0.81 to 1.5[a] (adalimumab vs. infliximab)	UCB Pharma-ceuticals and Agency for Healthcare Research and Quality
Jung et al.,[18] 2015 Korea Fair	Infliximab, Etanercept, Adalimumab	2005-2009 Health Insurance Review and Assessment Service	N = 8,421 • Etanercept: N = 3,955 • Infliximab: N = 2,012 • Adalimumab: N = 2,454	The study population comprised patients who were prescribed with TNF-α inhibitors from January 1, 2005-December 31, 2009.	Comparison between drugs showed a significantly lower incidence of tuberculosis in patients treated with etanercept (reference), highest incidence in those treated with: • Infliximab (IRR 6.8; 95% CI, 3.74 to 12.37)[a] • Adalimumab (IRR 3.45; 95% CI, 1.82 to 6.55)[a]	Korea Healthcare Technology, Ministry of Health and Welfare, Republic of Korea

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame Data Source	Sample Size	Population Characteristics	Harms	Funder
Singh et al.,[21] 2016 US Fair	Infliximab, Adalimumab, Certolizumab pegol NR Minimum of 6-month follow-up; median follow-up: 19 months	2006-2014 Claims data from Optum Labs Data Warehouse (includes privately insured and Medicare across US)	N = 3,205 • Infliximab: N = 1,427 • Adalimumab: N = 1,248 • Certolizumab pegol: n = 530	Inclusion criteria: a) ≥ 18 years of age, b) diagnosis of CD, c) > 6-month follow-up, d) prior 12 months no anti-TNF-α prescription Exclusion criteria: concomitant diagnosis of rheumatoid arthritis, ankylosing spondylitis, psoriasis, or psoriatic arthritis within the previous 12 months Baseline characteristics • Mean (SD) Age: ○ Infliximab 41 (15) ○ Adalimumab 40 (14) ○ Certolizumab pegol 41 (14) • % Male: ○ Infliximab 46% ○ Adalimumab 44% ○ Certolizumab 46%	Patients with 1-year baseline anti-TNF-α free period Infliximab vs adalimumab: The risk of serious infections was not significantly different (aHR 0.88; 95% CI, 0.48 to 1.64), n = 2,040 Infliximab vs certolizumab pegol: The risk of serious infections was not significantly different (aHR 0.47; 95%CI, 0.08 to 2.75), n = 506 Certolizumab pegol vs adalimumab: The risk of serious infections was not significantly different (aHR 2.06; 95% CI, 0.98 to 4.35), n = 1,046	American College of Gastro-enterology; National Institutes of Health
Singh et al.,[17] 2016 US Fair	Infliximab and adalimumab NR Minimum of 6-month follow-up after anti-TNF-α	2006-2014 Claims data from Optum Labs Data Warehouse (includes privately insured and Medicare across US)	N = 1400 • Infliximab: N= 1112 • Adalimumab: N = 288	Inclusion criteria: a) ≥ 18 years of age, b) diagnosis of UC, c) > 6 month follow-up, d) prior 12 months no anti-TNF-α prescription Exclusion criteria: concomitant diagnosis of rheumatoid arthritis, ankylosing spondylitis,	Patients with 1-year baseline anti-TNF-α free period (n = 816) Risk of serious infections (aHR 0.62; 95% CI, 0.29 to 1.34) was not significantly different between infliximab and adalimumab treated patients.	American College of Gastro-enterology Clinical Research; National Institutes of Health

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame Data Source	Sample Size	Population Characteristics	Harms	Funder
	initiation; median follow-up: 19 months			psoriasis, or psoriatic arthritis within the previous 12 months. <u>Baseline characteristics</u> Mean (SD) Age: • Infliximab 43 (16) • Adalimumab 42 (14) % Male: • Infliximab 52% • Adalimumab 52%		
Di Domeni-cantonio et al.,[13] 2018 Italy Rating?	Infliximab, Adalimumab Dosages unspecified Patients were followed from index date (date of prescription) until outcome, censoring at death, or at study end, which was 2 years from index date.	January 1, 2008-December 31, 2014 Hospital information system, payment exemptions register, regional drug claims register and the population registry	CD: • Infliximab: 367 analyzed • Adalimumab: 505 analyzed UC: • Infliximab: 469 analyzed • Adalimumab: 91 analyzed	Patients with UC (N = 560) and CD (N = 872) included in the prescription database between 2008 and 2014 who had new prescriptions for adalimumab or infliximab. Patients were not included if they were not registered in the regional health care system, diagnosis as unspecified IBD, discharged with diagnosis of other diseases with indications for anti- TNF-α therapy or evidence of drug therapies indicated for autoimmune diseases other than IBD in the past 24 months.	<u>N (%) with infusion reaction</u> CD: • Infliximab: 3 (0.8) • Adalimumab: 4 (0.8) UC: • Infliximab: 9 (1.9) • Adalimumab: 0 (0) <u>N (%) with acquired hemolytic anemias</u> CD: • Infliximab: 0 (0) • Adalimumab: 1 (0.2) UC: • Infliximab: 1 (0.2) • Adalimumab: 0 (0) No events of dermomiosytis or brain neoplasm were reported in any group. aHR (for infection: CD) 1.63; 95% CI, 0.61 to 4.34 (Infliximab vs. Adalimumab)	NR

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame Data Source	Sample Size	Population Characteristics	Harms	Funder
				Median (range): 41 (7 to 82) <u>N (%) female</u> UC • Infliximab: 197[a] (42.0) • Adalimumab: 52[a] (56.7) CD • Infliximab: 164[a] (44.7) • Adalimumab: 273[a] (54.1) Race/Ethnicity: NR	aHR (UC) 0.68; 95% CI, 0.19 to 2.44 (Infliximab vs. Adalimumab)	

Note. [a]Indicates a calculated value. Abbreviations: aHR: adjusted hazard ratio; CD: Crohn's disease; CI: confidence interval; IBD: irritable bowel disease; IRR: incident rate ratio; NR: not reported; SD: standard deviation; TNF: tumor necrosis factor; UC: ulcerative colitis; US: United States.

Appendix C. Evidence Grade Profiles

Table C1. Evidence Profile of Comparisons of Targeted Immune Modulators for Treatment of Crohn's Disease

Number of Studies/ Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Quality of the Evidence
Adalimumab Compared to Infliximab							
Quality of life (IBDQ)							
1 study[20]/73	RCT (switch)	Fair	NA	Indirect	Imprecise	IBDQ scores not different between groups	Very low[a]
Clinical improvement							
1 study[16]/20	RCT	Poor	NA	Direct	Imprecise	Endoscopic, clinical and histological recurrence not different between groups	Very low[b]
Overall adverse events							
1 study[20]/73	RCT	Fair	NA	Indirect	Imprecise	RR 1.14; 95% CI, 0.89 to 1.46	Very low[c]
Withdrawal due to adverse events							
1 study[20]/73	RCT	Fair	NA	Indirect	Imprecise	RR 6.17; 95% CI, 0.78 to 48.71	Very low[c]
Serious adverse events							
1 study[20]/73	RCT	Fair	NA	Indirect	Imprecise	RR 9.95; 95% CI, 0.57 to 174.1	Very low[c]
Infections							
1 study[13]/872[d]	Cohort	Fair	NA	Indirect	Imprecise	Incidence of infection (aHR 1.63; 95% CI, 0.61 to 4.34) for infliximab vs. adalimumab	Very low[e]
PF-04236921 Compared to Placebo							
Clinical improvement at 12 weeks (CDAI-70)							
1 study[15]/247	RCT	Fair	NA	Direct	Imprecise	Higher incidence with 50-mg dosage (47.4%) compared to placebo (28.6%); no difference in response between 10-mg dosage (35.2%) and placebo	Moderate[f]
Clinical remission at 12 weeks (CDAI < 150)							
1 study[15]/247	RCT	Fair	NA	Direct	Imprecise	Higher incidence for 50-mg dosage (27.4%), but not for 10-mg dosage (NR), compared to placebo (10.9%)	Low[g]
Quality of life (IBDQ) at 12 weeks							
1 study[15]/247	RCT	Fair	NA	Direct	Imprecise	No differences between either dosage and placebo	Low[g]

Number of Studies/ Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Quality of the Evidence
Overall adverse events at 12 weeks							
1 study[15]/247	RCT	Fair	NA	Direct	Imprecise	10 mg: RR 0.98; 95% CI, 0.88 to 1.10 50 mg: RR 0.89; 95% CI, 0.78 to 1.02	Moderate[f]
Serious adverse events at 12 weeks							
1 study[15]/247	RCT	Fair	NA	Direct	Imprecise	10 mg: RR 0.80; 95% CI, 0.32 to 2.0 50 mg: RR 0.97; 95% CI, 0.41 to 2.3	Low[g]
Withdrawals due to adverse events at 12 weeks							
1 study[15]/247	RCT	Fair	NA	Direct	Imprecise	10 mg: RR 0.88; 95% CI, 0.31 to 2.5 50 mg: RR 0.83; 95% CI, 0.30 to 2.4	Low[g]
Injection site reactions at 12 weeks							
1 study[15]/247	RCT	Fair	NA	Direct	Imprecise	50 mg: RR, 0.51; 95% CI, 0.10 to 2.7 10 mg: RR 1.70; 95% CI, 0.52 to 5.6	Low[g]
Adalimumab Compared to Certolizumab Pegol and Infliximab							
Serious infection							
1 study[21]/3,205	Cohort	Fair	NA	Indirect	Imprecise	The risk of serious infections was not significantly different among the three agents	Very low[e]
Adalimumab Compared to Etanercept and Infliximab							
Tuberculosis							
2 studies[18,19]/ 16,839	Cohort	Fair/Poor	Consistent	Indirect	Imprecise	Significantly higher incidence of tuberculosis with adalimumab (IRR 5.6 and 6.8) and infliximab compared to etanercept (IRR 4.9 and 5.6 respectively); similar incidence between adalimumab and infliximab	Very low[h]

Notes. [a]Downgraded for indirectness as all participants were on a tolerated regimen before randomization to continue infliximab or switch to adalimumab, which may not reflect usual clinical comparison, and for very serious imprecision; [b]Downgraded for study limitations and very serious imprecision; [c]Downgraded for indirectness as all participants were on a tolerated regimen before randomization to continue infliximab or switch to adalimumab, which may not reflect usual clinical comparison, and for very serious imprecision; [d]Sample size for the subgroup with Crohn's disease; [e]Started at low for study design, downgraded for indirectness due to use of administrative data and very serious imprecision; [f]Downgraded 1 level for imprecision; [g]Downgraded 2 levels for very serious imprecision;. [h]Started at low for study design, downgraded for indirectness due to use of administrative data, study limitations, and serious imprecision. Abbreviations. aHR: adjusted hazard ratio; CDAI: Crohn's Disease Activity Index; CI: confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; IRR: incident rate ratio; NA: not applicable; NR: not reported; RCT: randomized controlled trial; RR: relative risk.

Table C2. Evidence Profile of Comparisons of Targeted Immune Modulators for Treatment of Ulcerative Colitis

Number of Studies/ Patients	Design	Study Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Strength of the Evidence
Vedolizumab Compared to Adalimumab							
Clinical Remission at 1 year							
1 study[14]/769	RCT	Fair	NA	Direct	Imprecise	ARD 8.8% (95% CI, 2.5% to 15.0%)	Moderate[a]
Endoscopic remission at 1 year							
1 study[14]/769	RCT	Fair	NA	Direct	Imprecise	ARD 11.9% (95% CI, 5.3% to 18.5%)	Moderate[a]
Corticosteroid-free clinical remission (among those on steroids at baseline)							
1 study[14]/769	RCT	Fair	NA	Direct	Imprecise	ARD -9.3% (95% CI, -18.9% to 0.4%)	Low[b]
IBDQ score > 170 at 1 year							
1 study[14]/769	RCT	Fair	NA	Direct	Imprecise	ARD 9.6% (95% CI, 2.8% to 16.5%)	Moderate[a]
Overall adverse events at 1 year							
1 study[14]/769	RCT	Fair	NA	Direct	Imprecise	RR, 0.91(95% CI, 0.82 to 1.003)	Moderate[a]
Serious adverse events at 1 year							
1 study[14]/769	RCT	Fair	NA	Direct	Imprecise	RR, 0.80 (95% CI, 0.55 to 1.17)	Low[b]
Withdrawals due to adverse events at 1 year							
1 study[14]/769	RCT	Fair	NA	Direct	Imprecise	RR, 0.69 (95% CI, 0.38 to 1.25)	Low[b]
Infections at 1 year							
1 study[14]/769	RCT	Fair	NA	Direct	Imprecise	34.6/100 person-years vs. 23.4/100 person-years; *P* = .12)	Low[b]
Infliximab Compared to Adalimumab							
Serious Infection							
1 study[17]/1,400	Cohort	Fair	NA	Indirect	Imprecise	aHR, 0.62 (95% CI, 0.29 to 1.34)	Very low[c]
Infections							
1 study[13]/560	Cohort	Fair	NA	Indirect	Imprecise	aHR, 0.68 (95% CI, 0.19 to 2.44)	Very low[c]
Adalimumab Compared to Etanercept and Infliximab							
Harms							
2 studies [18,19] /16,839	Cohort	Fair (1) Poor (1)	Consistent	Indirect	Imprecise	Significantly higher incidence of tuberculosis with adalimumab (IRR, 5.6 and 6.8) and infliximab compared to etanercept (IRR, 4.9 and 5.6 respectively); similar incidence between adalimumab and infliximab.	Very low[d]

Notes: [a] Downgraded for imprecision. [b] Downgraded 2 levels for very serious imprecision. [c] Started at low for study design, downgraded for indirectness and imprecision. [d] Started at low for study design, downgraded for study limitations, indirectness, and imprecision. Abbreviations: aHR: adjusted hazard ratio; ARD: absolute risk difference; CI: confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; NA: not applicable; RCT: randomized controlled trial; RR: relative risk.

Appendix D. Instruments Used to Measure Outcomes in Trials of TIMs

Table D1. Instruments Used to Measure Outcomes in Trials of TIMs for Crohn's Disease and Ulcerative Colitis

Abbreviation	Name	Condition(s) Used In	General Description	Range and Direction
CDAI	Crohn's Disease Activity Index	CD	Eight clinical factors, each summed after adjustment with a weighting factor. These include: • Number of liquid or soft stools each day for 7 days x 2 • Abdominal pain (graded from 0-3 on severity) each day for 7 days x 5 • General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days x 7 • Presence of complications x 20 • Taking Lomotil or opiates for diarrhea x 30 • Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite) x 10 • Absolute deviation of Hematocrit from 47% in men and 42% in women x 6 • Percentage deviation from standard weight x 1	Lower numbers are better; values of 150 and less equal minimal disease; values above 150 equal active disease, and values above 450 equal extremely severe disease; CDAI 70 represents a decrease of 70 points or more.
CDEIS	Crohn's Disease Endoscopy Index of Severity	CD	Segment score averaged over segments on which data were available, ulcerated stenosis in any segment, and nonulcerated stenosis in any segment.	0-44, lower is better
EQ-5D	EuroQol 5-Dimension Assessment Instrument	All	Descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take 1 of 3 responses. The responses record 3 levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D dimension.	0-1, higher is better
IBDQ	Inflammatory Bowel Disease Questionnaire	CD and UC	32 questions grouped into 4 domains: bowel symptoms, systemic symptoms, emotional functioning, and social functioning	0-7, higher is better

Abbreviations. CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopy Index of Severity; EQ-5D: EuroQol 5-dimension assessment instrument; IBDQ: Inflammatory Bowel Disease Questionnaire; TIM: targeted immune modulators; UC: ulcerative colitis.

Appendix E. Detailed Results from Network Meta-Analyses

Table E1. Indirect Comparison Results from Network Meta-Analysis (Bonovas et al)[31]

	IFX	ADA	GLM	TFB
Clinical Response				
ADA	2.01 (1.36 to 2.98)[a]	-	-	-
GLM	1.67 (1.08 to 2.59)[a]	0.83 (0.55 to 1.26)	-	-
TFB	1.47 (0.89 to 2.43)	0.73 (0.45 to 1.19)	0.88 (0.53 to 1.48)	-
VDZ	1.12 (0.57 to 2.22)	0.56 (0.29 to 1.09)	0.67 (0.34 to 1.35)	0.76 (0.37 to 1.60)
Clinical Remission				
ADA	2.10 (1.21 to 3.64)[a]	-	-	-
GLM	1.43 (0.76 to 2.71)	0.68 (0.36 to 1.31)	-	-
TFB	1.63 (0.83 to 3.23)	0.78 (0.39 to 1.55)	1.14 (0.53 to 2.44)	-
VDZ	0.95 (0.33 to 2.74)	0.45 (0.16 to 1.31)	0.66 (0.22 to 2.02)	0.58 (0.19 to 1.82)
Mucosal Healing				
ADA	1.87 (1.26 to 2.79)[a]	-	-	-
GLM	1.75 (1.13 to 2.73)[a]	0.94 (0.61 to 1.43)	-	-
TFB	1.48 (0.83 to 2.65)	0.79 (0.45 to 1.40)	0.85 (0.46 to 1.54)	-
VDZ	1.05 (0.53 to 2.09)	0.56 (0.29 to 1.10)	0.60 (0.30 to 1.21)	0.71 (0.32 to 1.57)
Adverse Events				
ADA	1.31 (0.81 to 2.10)	-	-	-
GLM	1.28 (0.81 to 2.05)	0.98 (0.68 to 1.42)	-	-
TFB	1.54 (0.98 to 2.41)	1.18 (0.83 to 1.67)	1.20 (0.85 to 1.69)	-
VDZ	1.52 (0.88 to 2.62)	1.16 (0.73 to 1.85)	1.18 (0.75 to 1.87)	0.99 (0.64 to 1.54)
Serious Adverse Events				
ADA	0.89 (0.52 to 1.54)	-	-	-
GLM	0.83 (0.45 to 1.54)	0.93 (0.50 to 1.75)	-	-
TFB	1.04 (0.58 to 1.89)	1.17 (0.64 to 2.14)	1.26 (0.64 to 2.47)	-
VDZ	1.78 (0.89 to 3.55)	2.00 (0.99 to 4.02)	2.15 (1.00 to 4.59)[a]	1.71 (0.82 to 3.57)

Notes. Column drug is compared to row drug. OR (95% CI), ORs > 1.0 favor the column drug for efficacy measures, and ORs < 1.0 favor the column drug for safety outcomes. [a]Indicates a statistically significant association. Abbreviations. ADA: adalimumab; GLM: golimumab; IFX: infliximab; TFB: tofacitinib; VDZ: vedolizumab.

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